

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
18 October 2001 (18.10.2001)

PCT

(10) International Publication Number
WO 01/77289 A2(51) International Patent Classification⁷: C12N

(21) International Application Number: PCT/US01/10232

(22) International Filing Date: 29 March 2001 (29.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/195,605 6 April 2000 (06.04.2000) US(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87
Cambridge Park Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02460 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVAL-LIE, Edward, R.; 113 Ann Lee Road, Harvard, MA 01452 (US). COLLINS-RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). EVANS, Cheryl; 19236 Golden Meadow Drive, Germantown, MD 20876 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 38 Clarinda Park East, Dun Laoghaire, County Dublin (IE). AGOSTINO, Michael, J.; 26 Walcott Avenue, Andover, MA 01810 (US). BOWMAN, Michael, R.; 63 Gloucester Road, Westwood, MA (US). SPAULDING, Vikki; 47C Beatrice Street, Danville, NH (US). WONG, Gordon, G.; 239 Clark Road, Brookline, MA 02146 (US). CLARK, Hilary, F.; 495 Harkness Avenue, San Francisco, CA 94134 (US).

FECHTEL, Kim; 46 Marion Road, Arlington, MA 02174 (US). HOWES, Steven, H.; 37 Yerxa Road #2, No. 2, Cambridge, MA 02140 (US). RESNICK, Richard, J.; 36 Burnside Avenue, Somerville, MA 02144 (US). GULUKOTA, Kamalakur; 3 Stout Court, Lawrenceville, NJ 08648 (US). GRAHAM, James, R.; 40 Peirce Street, Arlington, MA 02476 (US).

(74) Agents: MANDRAGOURAS, Amy, E. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/77289 A2

(54) Title: POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

(57) Abstract: Isolated polynucleotides which have been derived from a variety of human tissue sources, and which encode novel secreted proteins, are provided. Also provided are methods for producing proteins using these polynucleotides, and the proteins so produced.

POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

RELATED APPLICATIONS

This application claims the benefit of prior-filed provisional patent application
5 U.S. Serial No. 60/195,605 entitled "Polynucleotides encoding Novel Secreted
Proteins", filed April 6, 2000. The content of the above-referenced application is
incorporated in its entirety.

FIELD OF THE INVENTION

10 The present invention provides novel polynucleotides and proteins encoded by
such polynucleotides, along with therapeutic, diagnostic and research utilities for these
polynucleotides and proteins.

BACKGROUND OF THE INVENTION

15 Gargantuan efforts have been employed by various investigational projects to
randomly sequence portions of naturally-occurring cDNAs. The rationale behind this
approach to identification and sequencing genes is founded in two basic principles: (1)
that transcribed cDNAs represent the product of the most important genes, namely
those that are actually expressed *in vivo*, and (2) that efforts to sequence genes and
20 other portions of the genome of target organisms which are not actually expressed
wastes substantial effort on areas not likely to yield genetic information of therapeutic
importance. Thus, the high-throughput sequencing efforts focus on only those portions
of the genome which are expressed. The randomly produced cDNA sequences
represent "expressed sequence tags" or "ESTs", which identify and can be used as
25 probes for the longer, full-length cDNA or genomic sequence from which they were
transcribed.

Although this "shortcut" approach to genomic sequencing presents savings of
effort compared to sequencing of the complete genome, it still produced a vast array of
ESTs which may not be directly useful as protein therapeutics. To date, the majority of
30 protein-related drug discovery has focused on the use of secreted proteins to produce a
desired therapeutic effect. Since the EST approach theoretically identifies all expressed
proteins, it produces an EST library which contains a mixture of secreted proteins (such
as hormones, cytokines and receptors) and non-secreted proteins (such as, for example,
metabolic enzymes and cellular structural proteins), without identifying which ESTs
35 correspond to proteins falling into either category. As a result, these methods are not
optimally tailored to the needs of investigators searching for secreted proteins because

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they must separate the secreted "wheat" from the non-secreted "chaff", wasting effort and resources in the process.

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the
5 past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning).

10 More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to
15 have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. Co-assigned U.S. Patent No. 5,536,637, which is incorporated herein by reference, provides methods for focusing genomic sequencing efforts on sequences encoding the secreted proteins which are of most interest for identification of protein therapeutics.
20 The '637 patent discloses a "signal sequence trap" which selectively identifies partial sequences encoding secreted proteins, namely "secreted expressed sequence tags" or "sESTs". The sequences of these sESTs can be used to design probes to isolate the full-length cDNA clones that encode secreted proteins.

It is to these secreted proteins and the full-length polynucleotides encoding
25 them that the present invention is directed.

SUMMARY OF THE INVENTION

The present invention provides for full-length cDNAs isolated from a variety of human RNA/cDNA sources which encode novel secreted proteins.

30 In preferred embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:
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NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID
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15 NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623;
or a complement of said sequence.

In other embodiments, the present invention provides an isolated
polynucleotide consisting of a nucleotide sequence selected from the group consisting
of:

20 SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID
NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID
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5 In further embodiments, the present invention provides an isolated polynucleotide consisting essentially of a nucleotide sequence selected from the group consisting of:

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SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID
NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623;

or a complement of said sequence.

30 In yet other embodiments, the present invention provides an isolated
polynucleotide comprising a nucleotide sequence which hybridizes to a sequence
selected from the group consisting of:

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The invention also provides for proteins encoded by the above-described polynucleotides. In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

- Processes are also provided for producing a protein, which comprise:
- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
 - (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention,

and/or a polynucleotide of the present invention, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

- 5 The nucleotide sequences of the isolated cDNAs of the present invention are reported in the Sequence Listing below. Table 2 lists the "Clone ID Nos." assigned by applicants to each SEQ ID NO: in the Sequence Listing.

Table 2

- 10 Each pair of entries in this table consists of the SEQ ID NO (e.g., 1, 2, etc.) followed by the Clone ID No. for such sequence (e.g., AA351_2, AA351_6, etc.).

1	AA351_2	201	MR315_1w	401	YB104_1	601	YCA1_1
2	AA351_6	202	NA1142_2	402	YB105_1	602	YCA2_1
3	AA36_21	203	NB31_13s	403	YB106_1	603	YCA3_1
4	AC423_6	204	NF61_3	404	YB107_1	604	YCA4_1
5	AJ180_4	205	NH369_4	405	YB108_1	605	YD100_1
6	AJ180_5	206	NH455_6	406	YB109_1	606	YD101_1
7	AJ1_1	207	NM190_1	407	YB10_1	607	YD102_1
8	AJ53_4	208	NN131_1	408	YB110_1	608	YD104_1
9	AK296_1is	209	NN93_1	409	YB111_1	609	YD105_1
10	AM1017_21	210	NN93_5	410	YB112_1	610	YD106_1
11	AM1083_14	211	NS121_9	411	YB113_1	611	YD108_1
12	AM224_1	212	NU232_3	412	YB114_1	612	YD110_1
13	AM340_11	213	NZ149_4	413	YB115_1	613	YD111_1
14	AM931_1is	214	O117_1	414	YB116_1	614	YD112_1
15	AP224_2s	215	OL1_1x	415	YB118_1	615	YD113_1
16	AP226_21	216	OM1_1x	416	YB119_1	616	YD114_1
17	AP259_1w	217	ON1_1x	417	YB120_1	617	YD115_1
18	AR325_2	218	ON2_1x	418	YB121_1	618	YD116_1
19	AR399_3	219	ON3_1x	419	YB122_1	619	YD117_1
20	AR440_1	220	OP1_1x	420	YB123_1	620	YD118_1
21	AS180_1	221	OR1_1	421	YB126_1	621	YD119_1
22	AS23_1	222	OR2_1	422	YB127_1	622	YD11_1
23	AS63_26	223	OR4_1	423	YB128_1	623	YD120_1
24	AS63_29	224	OR5_1	424	YB129_1		
25	AT211_1	225	OR6_1	425	YB130_1		

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26	AT211_17	226	OS1_1	426	YB131_1
27	AT340_23	227	PE246_4	427	YB132_1
28	AU106_1	228	PE567_1	428	YB133_1
29	AU107_1	229	PG284_1	429	YB134_1
30	AU118_1	230	PI13_1	430	YB135_1
31	AW92_1	231	PI13_10	431	YB136_1
32	AW92_1s	232	PI13_5	432	YB137_1
33	AX17_1	233	PI198_3	433	YB138_1
34	AX34_1	234	PJ11_2	434	YB140_1
35	AX34_3	235	PJ142_10	435	YB141_1
36	B224_1	236	PJ299_3	436	YB142_1
37	BA91_3	237	PK103_10	437	YB143_1
38	BD176_3	238	PK175_1	438	YB144_1
39	BD316_2	239	PK185_37	439	YB146_1
40	BD486_3	240	PK198_8	440	YB147_1
41	BD579_1w	241	PK224_1	441	YB148_1
42	BF245_1	242	PK224_11	442	YB149_1
43	BG219_2	243	PK224_12	443	YB14_1
44	BG241_1	244	PK224_9	444	YB151_1
45	BG457_1	245	PK259_5	445	YB152_1
46	BG72_1	246	PK266_4s	446	YB153_1
47	BI165_12	247	PK405_1	447	YB154_1
48	BK518_1w	248	PK558_1	448	YB155_1
49	BL196_22	249	PK65_1	449	YB156_1
50	BL229_22	250	PL16_12	450	YB157_1
51	BL249_18	251	PL211_2	451	YB158_1
52	BL255_1	252	PL251_1	452	YB159_1
53	BM41_3s	253	PL33_4	453	YB160_1
54	BN189_1	254	PL360_9	454	YB161_1
55	BN189_18	255	PL501_5	455	YB162_1
56	BO432_1	256	PL566_1s	456	YB163_1
57	BO432_4	257	PL772_2	457	YB165_1
58	BO538_2	258	PL85_3	458	YB166_1
59	BO549_1	259	PM303_10	459	YB167_1
60	BO71_1	260	PM347_4s	460	YB168_1
61	BP175_3	261	PM362_2	461	YB169_1
62	BP813_3	262	PM385_6	462	YB16_1

63	BR595_4	263	PM404_2	463	YB170_1
64	BR595_5	264	PM430_3	464	YB171_1
65	BS81_2	265	PM4_13s	465	YB172_1
66	BS81_2s	266	PM696_10	466	YB173_1
67	BV239_3	267	PP173_1	467	YB174_1
68	BV286_1	268	PP297_2	468	YB175_1
69	BV369_1w	269	PP314_19	469	YB176_1
70	BV370_1w	270	PP345_3	470	YB177_1
71	BV51_1	271	PP411_1	471	YB178_1
72	BZ16_3	272	PP509_3	472	YB17_1
73	BZ16_7	273	PT11_8	473	YB180_1
74	BZ53_1	274	PT215_3s	474	YB181_1
75	BZ644_34	275	PT217_3	475	YB182_1
76	CA106_19xs	276	PT285_20	476	YB184_1
77	CB98_4s	277	PT301_6	477	YB185_1
78	CC194_4	278	PT330_14	478	YB186_1s
79	CC288_9	279	PT35_11	479	YB188_1
80	CC346_1	280	PT364_2	480	YB189_1
81	CC403_3	281	PU234_2	481	YB18_1
82	CC412_1w	282	PU26_1	482	YB190_1
83	CC413_1w	283	PU26_3	483	YB191_1
84	CG158_1	284	PV138_2	484	YB194_1
85	CG432_1	285	PV323_2	485	YB195_1
86	CG432_2	286	PV549_2	486	YB198_1
87	CG432_3	287	PW102_9	487	YB199_1
88	CI247_3	288	PW123_7	488	YB1_1
89	CJ24_10	289	PW214_15s	489	YB200_1
90	CJ397_1	290	PW245_1	490	YB201_1
91	CJ84_3	291	PW328_4	491	YB202_1
92	CN1004_1w	292	PW378_2	492	YB203_1
93	CN173_1	293	PW429_13	493	YB205_1
94	CN238_1s	294	PW447_2	494	YB206_1
95	CO1256_1w	295	PW471_2	495	YB207_1
96	CO71_1	296	PX202_14	496	YB208_1
97	CO908_1	297	Q691_4x	497	YB209_1
98	CO908_41	298	QB216_2	498	YB20_1
99	CR1155_1	299	QB282_1	499	YB210_1

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102	CT702_8	302	QC525_1	502	YB213_1
103	CW675_3	303	QF17_1	503	YB214_1
104	CW691_11s	304	QF241_1	504	YB216_1
105	CZ770_1	305	QF2_1	505	YB217_1
106	CZ770_7	306	QF320_1	506	YB218_1
107	D329_1	307	QF464_7	507	YB220_1
108	D68_2	308	QG373_2	508	YB221_1
109	DA136_11	309	QG537_4	509	YB223_1
110	DA136_33	310	QG591_2	510	YB224_1
111	DA348_5	311	QM22_2	511	YB225_1
112	DA451_1	312	QU332_1	512	YB227_1
113	DA451_2	313	QV257_1	513	YB229_1
114	DD352_1	314	QV326_3	514	YB230_1
115	DD413_3	315	QV349_4	515	YB231_1
116	DE121_1w	316	QV378_2	516	YB232_1
117	DE122_1w	317	QX338_20	517	YB234_1
118	DF780_11	318	QY1263_1	518	YB236_1
119	DF835_1	319	QY1352_1	519	YB237_1
120	DH1349_1	320	QY1756_4	520	YB238_1
121	DH1361_1w	321	QY356_1	521	YB241_1
122	DI362_3	322	QY385_10	522	YB242_1
123	DI366_3	323	RA726_2	523	YB243_1
124	DI448_11	324	RB342_3	524	YB244_1
125	DK230_12	325	RB535_1	525	YB245_1
126	DK329_16	326	RB771_6	526	YB246_1
127	DK70_15	327	RB778_5	527	YB248_1
128	DN153_8	328	RB792_14	528	YB254_1
129	DN714_2	329	RD1058_2	529	YB260_1
130	DN721_8s	330	RD1111_2	530	YB261_1
131	DN732_1	331	RD207_1	531	YB27_1
132	DU160_15	332	RD309_2	532	YB32_1
133	DU238_1	333	RD616_11	533	YB41_1
134	DU238_1s	334	RD62_4	534	YB45_1
135	DU416_1	335	RD959_3	535	YB46_1
136	DU416_11	336	RG452_1	536	YB48_1

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137	DU416_2	337	RG661_1	537	YB4_1
138	DW1013_1w	338	RJ118_2	538	YB50_1
139	DX153_7	339	RJ402_4	539	YB52_1
140	EC428_2	340	RJ7_1	540	YB53_1
141	EE242_1w	341	RJ898_1	541	YB55_1
142	EH12_12	342	RJ900_18	542	YB59_1
143	EI16_13	343	WA153_2	543	YB61_1
144	EI16_13s	344	WA545_8	544	YB65_1
145	EI250_1	345	WA628_2	545	YB67_1
146	EJ254_1	346	WA628_5	546	YB68_1
147	EL15_14	347	WG67_19	547	YB6_1
148	EM446_1w	348	YD121_1	548	YB75_1
149	EN256_11	349	YD122_1	549	YB75_11
150	EN37_1	350	YA18_1	550	YB78_1
151	ET84_1	351	YA25_1	551	YB83_1
152	EZ265_1w	352	YA26_1	552	YB86_1
153	FG372_41	353	YA30_1	553	YB87_1
154	FG966_1w	354	YA31_1	554	YB92_1
155	FH6_12	355	YA33_1	555	YB93_1
156	FJ283_11s	356	YA34_1	556	YB94_1
157	FS185_1w	357	YA36_1	557	YB95_1
158	FX127_21	358	YA37_1	558	YB96_1
159	FX541_1w	359	YA39_1	559	YB97_1
160	FY356_14	360	YA3_1	560	YB98_1
161	FY641_1w	361	YA40_1	561	YB99_1
162	FZ87_2	362	YA45_1	562	YB9_1
163	G55_1	363	YA46_1	563	YBA1_1
164	GE553_1w	364	YA47_1	564	YBA2_1
165	GE554_1w	365	YA48_1	565	YC12_1
166	GX619_8	366	YA50_1	566	YC16_1
167	GX760_23	367	YA51_1	567	YC1_1
168	GY622_1w	368	YA52_1	568	YC21_1
169	H298_23	369	YA53_1	569	YC22_1
170	H541_3is	370	YA55_1	570	YC30_1
171	HC986_1	371	YA56_1	571	YC31_1
172	HZ162_4	372	YA57_1	572	YC32_1
173	IG35_12	373	YA58_1	573	YC33_1

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174	IJ1442_3	374	YA59_1	574	YC35_1
175	IK644_1w	375	YA5_1	575	YC36_1
176	IS114_1	376	YA60_1	576	YC37_1
177	J143_1	377	YA61_1	577	YC38_1
178	J218_15	378	YA62_1	578	YC39_1
179	K289_4	379	YA63_1	579	YC3_1
180	K421_1x	380	YA64_1	580	YC41_1
181	K446_3	381	YA68_1	581	YC42_1
182	K511_1is	382	YA71_1	582	YC43_1
183	KJ921_1w	383	YA72_1	583	YC44_1
184	KM14_4	384	YA73_1	584	YC45_1
185	KZ316_1w	385	YA74_1	585	YC46_1
186	LF307_5	386	YA76_1	586	YC47_1
187	LR607_12	387	YA78_1	587	YC50_1
188	LT390_9	388	YA79_1	588	YC51_1
189	LT403_2	389	YA81_1	589	YC52_1
190	LT706_1w	390	YA82_1	590	YC54_1
191	LU524_2	391	YA83_1	591	YC55_1
192	M141_1	392	YA84_1	592	YC56_1
193	MA278_1w	393	YA85_1	593	YC57_1
194	MD312_1	394	YA8_1	594	YC58_1
195	ME514_7	395	YAA1_1	595	YC59_1
196	ME796_1	396	YAA2_1	596	YC5_1
197	ML227_1	397	YAA3_1	597	YC61_1
198	MM197_1	398	YB100_1	598	YC62_1
199	MM367_6	399	YB102_1	599	YC63_1
200	MN341_2	400	YB103_1	600	YC64_1

The "Clone ID No." for a particular clone consists of one or two letters followed by a number. The letters designate the tissue source from which the sEST for that clone was initially isolated. Table 3 below lists the various sources which were run through applicants' signal sequence trap.

TABLE 3

	Sel.	Species		Stage Tissue	Cell Type	Treatment
5	AA	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
	AC	Human	Fetal	Placenta	26yrs., 1 specimen	None
	AJ	Human	Adult	Testes	10-61yrs., pool of 11	None
	AK	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
	AM	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
10	AP	Human	Fetal	Placenta	26yrs., 1 specimen	None
	AR	Human	Adult	Retina	16-75yrs., pool of 76	None
	AS	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	AT	Human	Adult	Blood	Lymphocytes+Dendritic Cells	MLR
	AU	Human	Adult	Testes	10-61yrs., pool of 11	None
15	AW	Human	Adult	Ovary	PA-1 Teratocarcinoma line	RA+activin
	AX	Human	Adult	Testes	10-61yrs., pool of 11	None
	B	Human	Adult	Blood	PBMC	ConA + PMA
	BA	Human	Fetal	Placenta	26yrs., 1 specimen	None
	BD	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
20	BF	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	BG	Human	Adult	Brain	N/A	None
	BI	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
	BK	Human	Adult	Retina	16-75yrs., pool of 76	None
	BL	Human	Adult	Testes	10-61yrs., pool of 11	None
25	BM	Human	Adult	Muscle	N/A	None
	BN	Human	Fetal	Placenta	26yrs., 1 specimen	None
	BO	Human	Adult	Retina	16-75yrs., pool of 76	None
	BP	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
	BR	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
30	BS	Human	Adult	Pituitary	N/A	None
	BV	Human	Adult	Brain	N/A	None
	BZ	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
	CA	Mouse	Fetal	Embryo	ES line embryoid bodies	2-12d post LIF
	CB	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
35	CC	Human	Adult	Brain	N/A	None
	CG	Human	Adult	Testes	10-61yrs., pool of 11	None
	CI	Human	Adult	Brain	N/A	None
	CJ	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	CN	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
40	CO	Human	Adult	Brain	N/A	None
	CR	Human	Adult	Testes	10-61yrs., pool of 11	None
	CT	Human	Adult	Brain	N/A	None
	CW	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	CZ	Human	Adult	Testes	10-61yrs., pool of 11	None
45	D	Human	Adult	Blood	PBMC	ConA + PMA
	DA	Human	Fetal	Placenta	26yrs., 1 specimen	None
	DD	Human	Adult	Testes	10-61yrs., pool of 11	None
	DE	Human	Adult	Testes	Teratocarcinoma NCCIT line	None

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	DF	Human	Adult	Brain	N/A	None
	DH	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	DI	Human	Adult	Testes	10-61yrs., pool of 11	None
	DK	Human	Fetal	Kidney	N/A	None
5	DN	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	DU	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	DW	Human	Adult	Brain	N/A	None
	DX	Human	Adult	Testes	10-61yrs., pool of 11	None
	EC	Human	Adult	Brain	N/A	None
10	EE	Human	Adult	Testes	10-61yrs., pool of 11	None
	EH	Human	Adult	Blood	PBMC	G-CSF in vivo
	EI	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	EJ	Human	Fetal	Placenta	26yrs., 1 specimen	None
	EL	Human	Adult	Testes	10-61yrs., pool of 11	None
15	EM	Human	Fetal	Kidney	N/A	None
	EN	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	ET	Human	Adult	Testes	10-61yrs., pool of 11	None
	EZ	Human	Fetal	Kidney	N/A	None
	FG	Human	Adult	Brain	N/A	None
20	FH	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	FJ	Human	Adult	Lung	Carcinoma line	None
	FS	Human	Adult	Testes	10-61yrs., pool of 11	None
	FX	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	FY	Human	Fetal	Placenta	26yrs., 1 specimen	None
25	FZ	Human	Fetal	Placenta	26yrs., 1 specimen	None
	G	Human	Adult	Blood	PBMC	ConA + PMA
	GE	Human	Adult	Brain	N/A	None
	GX	Human	Adult	Brain	N/A	None
	GY	Human	Adult	Testes	10-61yrs., pool of 11	None
30	H	Human	Adult	Blood	PBMC	PHA+PMA+MLR
	HC	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	HZ	Human	Adult	Brain	Thalamus	None
	IG	Human	Adult	Testes	10-61yrs., pool of 11	None
	IJ	Human	Adult	Blood	PBMC	G-CSF in vivo
35	IK	Human	Adult	Retina	Retinoblastoma Y79 line	None
	IS	Human	Adult	Trachea	N/A	None
	J	Human	Adult	Blood	PBMC	PHA+PMA+MLR
	K	Mouse	Adult	Bone Marrow	Stromal line FCM-4	None
	KJ	Human	Fetal	Brain	N/A	None
40	KM	Human	Adult	Retina	Retinoblastoma Y79 line	None
	KZ	Human	Adult	Retina	16-75yrs., pool of 76	None
	LF	Human	Adult	Spinal Cord	N/A	None
	LR	Human	Adult	Lymph Node	N/A	None
	LT	Human	Adult	Retina	Retinoblastoma Y79 line	None
45	LU	Human	Adult	Retina	Retinoblastoma Y79 line	None
	M	Human	Adult	Neural	Glioblastoma line T98G	None

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	MA	Human	Fetal	Carcinoma	NTD2-1 line	None
	MD	Human	Fetal	Kidney	N/A	None
	ME	Human	Adult	Brain	Substantia Nigra	None
	ML	Human	Adult	Brain	Caudate Nucleus	None
5	MM	Human	Adult	Retina	WERI-Rb1 retinoblastoma line	None
	MN	Human	Adult	Brain	Hippocampus	None
	MR	Human	Adult	Testes	N/A	None
	NA	Human	Adult	Brain	Corpus Callosum	None
	NB	Human	Adult	Spinal Cord	N/A	None
10	NF	Human	Adult	Brain	Substantia Nigra	None
	NH	Human	Adult	Brain	Thalamus	None
	NM	Human	Adult	Blood	Erythroleukemia TF-1 line	None
	NN	Human	Adult	Kidney	293 embryonal carcinoma line	None
	NS	Human	Adult	Retina	WERI-Rb1 retinoblastoma line	None
15	NU	Human	Adult	Brain	Caudate Nucleus	None
	NZ	Human	Adult	Blood	Erythroleukemia TF-1 line	None
	O	Human	Adult	Blood	Dendritic Cells	None
	OL	Mouse	Adult	Lymphocyte	Pro-B line FLEB14	None
	OM	Mouse	Adult	Brain	Glioma line T98G	IL-1
20	ON	Mouse	Adult	Brain	Glioma line T98G	IL-1
	OP	Mouse	Adult	Brain	Glioma line T98G	IL-1
	OR	Human	Adult	Brain	Glioma line T98G	IL-1
	OS	Human	Fetal	UC	Endothelial line HUV-EC-C	None
	PE	Human	Adult	Blood	K562 chronic ML line	None
25	PG	Human	Adult	Thyroid	N/A	None
	PI	Human	Adult	Thyroid	N/A	None
	PJ	Human	Adult	Testes	EC NT2D1 line	RA for 23 days
	PK	Human	Adult	Kidney	293 embryonal carcinoma line	None
	PL	Human	Adult	Kidney	293 embryonal carcinoma line	None
30	PM	Human	Adult	Kidney	293 embryonal carcinoma line	None
	PP	Human	Adult	Blood	LL MOLT-4 line	None
	PT	Human	Adult	Blood	LL MOLT-4 line	None
	PU	Human	Adult	Blood	PL HL-60 line	None
	PV	Human	Adult	Brain	Cerebellum	None
35	PW	Human	Adult	Brain	Cerebellum	None
	PX	Human	Adult	Brain	Cerebellum	None
	Q	Mouse	Adult	Bone Marrow	N/A	5 fluoro-uracil
	QB	Human	Adult	Bladder	5637 carcinoma line	None
	QC	Human	Adult	Neural	Neuroepithelioma HTB-10 line	None
40	QF	Human	Adult	Bladder	5637 carcinoma line	None
	QG	Human	Adult	Neural	Neuroepithelioma HTB-10 line	None
	QM	Human	Adult	Blood	Histiocytic lymphoma U937 line	None
	QU	Human	Adult	Blood	K562 chronic ML line	None
	QV	Human	Adult	Testes	EC NT2D1 line	RA for 23 days
45	QX	Human	Adult	Bone	RD-ES line	None
	QY	Human	Adult	Blood	PL HL-60 line	None

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	RA	Human	Adult	Brain	Substantia Nigra	None
	RB	Human	Adult	Kidney	293 embryonal carcinoma line	None
	RD	Human	Adult	Kidney	293 embryonal carcinoma line	None
	RG	Human	Adult	Blood	PL HL-60 line	None
5	RJ	Human	Adult	Neural	Neuroepithelioma HTB-10 line	None
	WA	Xenopus	Fetal	Embryo	Dorsal Mesoderm	None
	WG	Xenopus	Fetal	Embryo	Dorsal Mesoderm	None
	YA	Human	Adult	Testes	10-61yrs., pool of 11	None
	YAA	Human	Adult	Bone	Osteosarcoma MG63 line	None
10	YB	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	YBA	Human	Adult	Lymph Node	N/A	None
	YC	Human	Adult	Kidney	293 embryonal carcinoma line	None
	YCA	Human	Adult	Thymus	N/A	None
	YD	Human	Adult	Brain	N/A	None

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Table 3 Cell Type and Treatment Key:

	2-12d post LIF:	2-12 days after LIF removal
	ConA:	concanavalin A
	EC:	Embryonal Carcinoma
20	G-CSF:	granulocyte-colony stimulating factor
	LL:	Lymphoblastic Leukemia
	ML:	myelogenous leukemia
	MLR:	mixed lymphocyte reaction
	PHA:	phytohemagglutinin
25	PL:	Promyelocytic Leukemia
	PMA:	phorbol myristate acetate
	PMBC:	peripheral blood mononuclear cells
	RA:	retinoic acid
	RA+activin:	Pool of RA-treated + activin-treated + untreated tissue
30	UC:	Umbilical Cord

Thus, the tissue source for a particular sEST sequence can be identified in Table 3 by the one and two letter designations used in the relevant "Clone ID No." in Table 2. For example, a sEST designated as "PP85" would have been isolated from a human adult blood (lymphoblastic leukemia MOLT-4) library (i.e., selection "PP") as indicated in Table 3. These sEST sequences were then used to isolate the full-length cDNA clones listed in Table 2; these full-length cDNA clones are generally human cDNA clones as described in the Sequence Listing appended hereto.

As used herein, "polynucleotide" includes single- and double-stranded RNAs, DNAs and RNA:DNA hybrids.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic

materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can then be performed at an Internet site provided by the National Center for Biotechnology Information having the address www.ncbi.nlm.nih.gov/UniGene, in order to identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250- 254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et*

al., 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* 266: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* 215: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, *Nature Genetics* 3: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in

molecular sequences, *Proc. Natl. Acad. Sci. USA* **90**: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from the Internet file-transfer protocol (FTP) site <ftp://blast.wustl.edu/blast/executables>. The complete suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated

from mammalian species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadryas*, *Cercopithecus aethiops*, *Cebus capucinus*, *Aotus trivirgatus*, *Sanguinus oedipus*,
5 *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Oryctolagus cuniculus*, *Bos taurus*, *Ovis aries*, *Sus scrofa*, and *Equus caballus*, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species
10 (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682- 690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

15 The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at
20 least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from
25 individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most
30 preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M- R.

35

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [†]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T _B *; 1xSSC	T _B *; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T _D *; 1xSSC	T _D *; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T _F *; 1xSSC	T _F *; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T _H *; 4xSSC	T _H *; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T _J *; 4xSSC	T _J *; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T _L *; 2xSSC	T _L *; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T _N *; 6xSSC	T _N *; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T _P *; 6xSSC	T _P *; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T _R *; 4xSSC	T _R *; 4xSSC

†: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6(log₁₀[Na⁺]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et

al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may contain sequences at its 5' and/or 3' end that are derived from linker, polylinker, or multiple cloning site sequences commonly found in vectors such as the pMT2 or pED expression vectors (see below). For example, sequences such as SEQ ID NO:626, SEQ ID NO:627, or SEQ ID NO:628 may be found at the 5' end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 3' end. Similarly, sequences such as SEQ ID NO:629, SEQ ID NO:630, or SEQ ID NO:631 may be found at the 3' end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 5' end. In addition, variants of these linker sequences may be present in isolated polynucleotides of the invention, which linker variants vary from SEQ ID NO:626 through SEQ ID NO:631 by the alteration, insertion, or deletion of one or more nucleotides. Therefore, a preferred embodiment of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 25 and ending at nucleotide (N-25) of the SEQ ID NO for that polynucleotide, where N represents the total number of nucleotides in the sequence. As a specific example, a preferred embodiment of the invention comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 25 to nucleotide 1616, where the total number of nucleotides (N) in SEQ ID NO:1 is 1641, and N-25 equals 1616. More preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 30 and ending at nucleotide (N-30) of the SEQ ID NO for that polynucleotide. Most preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 35 and ending at nucleotide (N-35) of the SEQ ID NO for that polynucleotide. Similarly, additional embodiments are those nucleotide sequences that extend from nucleotide 40 to nucleotide (N-40), or from nucleotide 45 to nucleotide (N-45), or from nucleotide 50 to nucleotide (N-50), or from nucleotide 60 to nucleotide (N-60), or from nucleotide 65 to

nucleotide (N-65), or from nucleotide 70 to nucleotide (N-70), or from nucleotide 75 to nucleotide (N-75), or from nucleotide 80 to nucleotide (N-80), etc., for any of the polynucleotides disclosed herein. Further preferred embodiments are those nucleotide sequences that are subsequences of the nucleotide sequences disclosed herein, beginning at any nucleotide position selected from the group consisting of nucleotide 5, nucleotide 10, nucleotide 15, nucleotide 20, nucleotide 25, nucleotide 30, nucleotide 35, nucleotide 40, nucleotide 45, nucleotide 50, nucleotide 55, nucleotide 60, nucleotide 65, nucleotide 70, nucleotide 75, or nucleotide 80, and ending at any nucleotide position selected from the group consisting of nucleotide (N-5), nucleotide (N-10), nucleotide (N-15), nucleotide (N-20), nucleotide (N-25), nucleotide (N-30), nucleotide (N-35), nucleotide (N-40), nucleotide (N-45), nucleotide (N-50), nucleotide (N-55), nucleotide (N-60), nucleotide (N-65), nucleotide (N-70), nucleotide (N-75), or nucleotide (N-80), wherein N is the total number of nucleotides disclosed for a particular SEQ ID NO.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the

appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin- toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, MA), Pharmacia (Piscataway, NJ) and Invitrogen Corporation (Carlsbad, CA), respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from the Eastman Kodak Company (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

5 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,
10 including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

 The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are
15 naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may
20 be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

25 Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

30

USES AND BIOLOGICAL ACTIVITY

 The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the
35 present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The primary use of polynucleotides of the invention which are sESTs is as probes for the identification and isolation of full-length cDNAs and genomic DNA molecules which correspond (i.e., is a longer polynucleotide
5 cDNAs and genomic DNA molecules which correspond (i.e., is a longer polynucleotide sequence of which substantially the entire sEST is a fragment in the case of a full-length cDNA, or which encodes the sEST in the case of a genomic DNA molecule) to such sESTs. Techniques for use of such sequences as probes for larger cDNAs or genomic molecules are well known in the art.

10 The polynucleotides can also be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify
15 chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract- out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers
20 for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the
25 polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to
30 determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a
35 particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand

interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

- 5 Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, 10 Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

- 15 Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a 20 separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

25 Cytokine and Cell Proliferation/Differentiation Activity

- A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one 30 or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, 35 Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature* 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, *Immunologic studies in Humans*); Weinberger et al., *Proc. Natl. Acad. Sci. USA* 77:6091-6095, 1980; Weinberger et al., *Eur. J. Immun.* 11:405-

411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

5 A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B
10 lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including
15 infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present
20 invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye
25 disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses,
30 in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires
35 continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure

to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including
5 without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*,
preventing high level lymphokine synthesis by activated T cells, will be useful in
situations of tissue, skin and organ transplantation and in graft-versus-host disease
(GVHD). For example, blockage of T cell function should result in reduced tissue
10 destruction in tissue transplantation. Typically, in tissue transplants, rejection of the
transplant is initiated through its recognition as foreign by T cells, followed by an
immune reaction that destroys the transplant. The administration of a molecule which
inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on
immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity
15 alone or in conjunction with a monomeric form of a peptide having an activity of
another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to
transplantation can lead to the binding of the molecule to the natural ligand(s) on the
immune cells without transmitting the corresponding costimulatory signal. Blocking B
lymphocyte antigen function in this matter prevents cytokine synthesis by immune
cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of
20 costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance
in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking
reagents may avoid the necessity of repeated administration of these blocking reagents.
To achieve sufficient immunosuppression or tolerance in a subject, it may also be
necessary to block the function of a combination of B lymphocyte antigens.

25 The efficacy of particular blocking reagents in preventing organ transplant
rejection or GVHD can be assessed using animal models that are predictive of efficacy
in humans. Examples of appropriate systems which can be used include allogeneic
cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which
have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins
30 *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*,
Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD
(see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847)
can be used to determine the effect of blocking B lymphocyte antigen function *in vivo*
on the development of that disease.

35 Blocking antigen function may also be therapeutically useful for treating
autoimmune diseases. Many autoimmune disorders are the result of inappropriate
activation of T cells that are reactive against self tissue and which promote the

production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit

5 T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal

10 models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

15 Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function

20 may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral

25 antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that

30 the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor

35 immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-

specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982;

Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

- 5 Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto.
- 10 1994.

- Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan,
- 15 A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

- 20 Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., *Journal of Experimental Medicine* 173:549-559, 1991; Macatonia et al., *Journal of Immunology* 154:5071-5079, 1995; Porgador et al., *Journal of Experimental Medicine* 182:255-260,
- 25 1995; Nair et al., *Journal of Virology* 67:4062-4069, 1993; Huang et al., *Science* 264:961-965, 1994; Macatonia et al., *Journal of Experimental Medicine* 169:1255-1264, 1989; Bhardwaj et al., *Journal of Clinical Investigation* 94:797-807, 1994; and Inaba et al., *Journal of Experimental Medicine* 172:631-640, 1990.

- Assays for lymphocyte survival/apoptosis (which will identify, among others,
- 30 proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., *Cytometry* 13:795-808, 1992; Gorczyca et al., *Leukemia* 7:659-670, 1993; Gorczyca et al., *Cancer Research* 53:1945-1951, 1993; Itoh et al., *Cell* 66:233-243, 1991; Zacharchuk, *Journal of Immunology* 145:4037-4045, 1990; Zamai et al., *Cytometry*
- 35 14:891-897, 1993; Gorczyca et al., *International Journal of Oncology* 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

5

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama *et al.*, Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben *et al.*, Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A

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protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured
5 by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

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Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or
15 endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in
20 improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a
25 population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or
30 prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience
35 (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. *J. Clin. Invest.* 95:1370-1376, 1995; Lind et al. *APMIS* 103:140-146, 1995; Muller et al. *Eur. J*

Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

5 A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or
10 inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

15 Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

20 Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands,
25 receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the
30 relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

35 Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell
5 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells
10 involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to
15 treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine- induced lung injury, inflammatory bowel disease, Crohn's
20 disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

25 In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support
30 tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

35 A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other

parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

20 ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular

cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

5 A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

 The pharmaceutical composition of the invention may be in the form of a
10 complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and
15 structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies
20 able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

 The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which
25 exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S.
30 Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

 As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or
35 amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When

applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a
5 therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more
10 cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with
15 cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or
20 cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the
25 pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean
30 oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present
35 invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due
5 regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as
10 known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the
15 condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be
20 administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μ g to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1 μ g to about 1 mg) of protein of the present invention per kg
25 body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present
30 invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain
35 polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at

the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of

the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

5 Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

10 A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include
15 hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so
20 much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue
25 in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to
30 humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size
35 of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other

proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

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2. An isolated polynucleotide consisting of a nucleotide sequence selected from the group consisting of:

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NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623;
or a complement of said sequence.

15

3. An isolated polynucleotide comprising a nucleotide sequence which
hybridizes to a sequence selected from the group consisting of:

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- 71 -

SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623; or to a complement of said sequence.

5 4. The polynucleotide of any one of claims 1-3, wherein said polynucleotide is operably linked to at least one expression control sequence.

 5. A vector comprising the polynucleotide of claim 4.

10 6. A host cell transformed with a vector comprising the polynucleotide of any one of claims 1-3.

 7. A process for producing a protein encoded by the polynucleotide of claim 4, which process comprises:

15 (a) growing a culture of a host cell in a suitable culture medium, wherein the host cell has been transformed with the polynucleotide of claim 4; and
 (b) purifying said protein from the culture.

 8. A protein produced according to the process of claim 7.

20 9. An antibody that specifically binds to the protein of claim 8.

 10. A method for detecting the protein of claim 8, comprising contacting a sample suspected of containing the protein with an antibody that specifically binds to
25 the protein, under conditions such that the antibody binds the protein and the protein is detected.

 11. A method for detecting the polynucleotide of any one of claims 1-3, comprising contacting a sample suspected of containing the polynucleotide with a
30 polynucleotide reagent that hybridizes to the polynucleotide, under conditions such that the reagent binds the polynucleotide and the polynucleotide is detected.

 12. The method of claim 10 or 11, wherein the sample is a biological sample.

35 13. The method of claim 12, where the biological sample is isolated from a human.

14. A method of identifying a compound that modulates the activity of the protein of claim 8, comprising contacting a composition comprising the protein with a test compound and monitoring the effect of the test compound on the activity of the protein, such that a modulatory compound is identified.

5

15. A method of identifying a compound that modulates the expression of the polynucleotide of any one of claims 1-3, comprising contacting a cell that expresses the polynucleotide with a test compound and determining the effect of the test compound on the expression of the polynucleotide, such that a modulatory compound is identified.

10

16. A method of identifying a compound that modulates the production of the protein of claim 8, comprising contacting a cell that produces the protein with the test compound and determining the effect of the test compound on the production of the protein, such that a modulatory compound is identified.

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17. A method of treating a subject having a disorder characterized by aberrant expression of the polynucleotide of any one of claims 1-3, comprising administering to said subject a therapeutically effective amount of a compound that modulates expression of the polypeptide, such that treatment is effected.

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18. A method of treating a subject having a disorder characterized by aberrant production of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates production of the protein, such that treatment is effected.

25

19. A method of treating a subject having a disorder characterized by aberrant activity of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates activity of the protein, such that treatment is effected.

30

SEQUENCE LISTING

<110> Jacobs, Kenneth
 McCoy, John M.
 LaVallie, Edward R.
 Collins-Racie, Lisa A.
 Evans, Cheryl
 Merberg, David
 Treacy, Maurice
 Agostino, Michael J.
 Steininger II, Robert J.
 Bowman, Michael R.
 Spaulding, Vikki
 Wong, Gordon G.
 Clark, Hilary
 Fechtel, Kim
 Howes, Steven H.
 Resnick, Richard J.
 Gulukota, Kamalakar
 Graham, James R.
 Genetics Institute, Inc.

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<210> 9

<211> 1197

<212> DNA

<213> Homo sapiens

<400> 9

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<210> 10

<211> 2660

<212> DNA

<213> Homo sapiens

<400> 10

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<210> 11

<211> 1647

<212> DNA

<213> Homo sapiens

<400> 11

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<210> 12

<211> 1467

<212> DNA

<213> Homo sapiens

<400> 12

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<210> 13

<211> 815

<212> DNA

<213> Homo sapiens

<400> 13

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<210> 14

<211> 779

<212> DNA

<213> Homo sapiens

<400> 14

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<210> 15

<211> 1230

<212> DNA

<213> Homo sapiens

<400> 15

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<211> 1135

<212> DNA

<213> Homo sapiens

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<210> 17

<211> 2950

<212> DNA

<213> Homo sapiens

<400> 17

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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 19

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<211> 1305

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<213> Homo sapiens

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<211> 3580

<212> DNA

<213> Homo sapiens

<400> 21

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<211> 783

<212> DNA

<213> Homo sapiens

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<210> 24

<211> 1724

<212> DNA

<213> Homo sapiens

<400> 24

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<210> 25

<211> 1070

<212> DNA

<213> Homo sapiens

<400> 25

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<211> 2496

<212> DNA

<213> Homo sapiens

<400> 26

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<210> 27

<211> 986

<212> DNA

<213> Homo sapiens

<400> 27

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<210> 28

<211> 212

<212> DNA

<213> Homo sapiens

<400> 28

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<210> 29

<211> 11

<212> DNA

<213> Homo sapiens

<400> 29

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<210> 30

<211> 386

<212> DNA

<213> Homo sapiens

<400> 30

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<210> 31

<211> 3104

<212> DNA

<213> Homo sapiens

<400> 31

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<210> 32

<211> 3104

<212> DNA

<213> Homo sapiens

<400> 32

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<210> 33

<211> 72

<212> DNA

<213> Homo sapiens

<400> 33

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atggcctaca gg 72

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<210> 34

<211> 1038

<212> DNA

<213> Homo sapiens

<400> 34

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gggagtgttg gtgacggggg aggcataagg ggtgagagt ctgataagaa ggatgaggag 180
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caattcaatc gggaatg 1038

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<210> 35

<211> 687

<212> DNA

<213> Homo sapiens

<400> 35

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tcccgattga attgcccgg ctcagcccaa gtctgaatt tttcacagt aacttgtctc 60
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cacacctcga ctttggcctt caactgcccc agggccccag gggctgcctc agcccttagt 180
gggtctttct cgtccggggg ccccggttca gcacccatag agtcaggctc atccagggga 240
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<210> 36

<211> 960

<212> DNA

<213> Homo sapiens

<400> 36

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tggtatataa acaacttta agaaagatca ttatcctttt ctctacctaa atatgaggag 780
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<210> 37

<211> 684

<212> DNA

<213> Homo sapiens

<400> 37

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<210> 38

<211> 1510

<212> DNA

<213> Homo sapiens

<400> 38

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cgccgctttt tttttttttt tttttttttt tttttttttt tttttttttt aatttnggta 60
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attattgcaa gtgttctaaa aaatcagaac aaaactaatt tattatagtt ctgtcttcat 180
tataccacac gtgttggtga gttaaacaca acaaaattgt cttttctttt aaaagtgtct 240
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atatacatat ttctattgcc tgttagcttg ttctaagcct ctttaactat tacaacaaaa 360
aaaaaaaaag gaaagaaaaa gaaaattcat tgtttaaagg caaacattca attcagttga 420
tacaacatta cagtacagtc aactaacatc attcaacgaa ggtaacaagt ctagccttag 480
cttcttgagt taaaagtcta tagaccagat tgctacaaaa gtttcaatgc tgcttcaaaa 540
ccgtatgta gctttttgga ggacaaaagta ctttctacgg atggcttcag aagggtcat 600
gctactggta aaagcacagg ggaaccccat cctgtcatta atcattttat tgagcactgt 660
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<210> 39

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 39

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tttaatatagac ttatatttta aagcttaaaa ataatttagc ttctagagta ttacgttttt 180
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tcactctgta ttcttatca gatagtaagt aacctgtaag tttggagtat tactgttttc 1260
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<210> 40

<211> 1659

<212> DNA

<213> Homo sapiens

<400> 40

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ggagccgagc tttagaccca ctgctaagga gttattgaag cacaagttaa tactacgcaa 180
tgcaaagaaa acttctact tgaccgagct catcgacagg tacaagagat ggaaggccga 240
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ggggggcagt gattctgggg actggatctt cacaatccga gaaaaagatc ccaagaatct 360
cgagaatgga gctcttcagc catcggactt ggacagaaat aagatgaaag acatcccaaa 420
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aatacgattt tctgttgcaac cttgtagtgg attctgcata tcatctttcc cacctaaaaa 1620
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<210> 41

<211> 334

<212> DNA

<213> Homo sapiens

<400> 41

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acgcctttct gttccttgct ctcaccttac tcccctcagg accctacccc accctctttg 180
aaaagacaaa gctctgccta catagaagac tttttttatt ttaaccaaag ttactgttgt 240
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cgggatgcca catttcataa ctgttttttaa tgggt 334

```

<210> 42

<211> 2456

<212> DNA

<213> Homo sapiens

<400> 42

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aataccaagt gtcagcatgt tagtaataaa caggtgtctc taccattagt caaagggtggg 180
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<210> 43

<211> 698

<212> DNA

<213> Homo sapiens

<400> 43

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caaatgacc aatctgaaat tagaggatgc aaggagag 698

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<210> 44

<211> 1346

<212> DNA

<213> Homo sapiens

<400> 44

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gatctgcgga agtaaccaca aaatattatc gaaaaaagaa aagaattcta atgaccagcc 300
gtgaatgtgt agggttgcag ctctattctc caaaactgta ggaacttgac ttgcgttaga 360
gtgtactctg aaaccaactc gtctctggcc gcaggagtct atatgttttc gtaatcttca 420
tcaagaagtt tttaaaaggc aagcaaaaac agaagcaaat catatcaaac ggggatagaa 480
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ccttgggatt tttttttttt gttttcccta acaatttgga cactacaatt gctctcacia 720
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<210> 45

<211> 1908

<212> DNA

<213> Homo sapiens

<400> 45

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<210> 46

<211> 1725

<212> DNA

<213> Homo sapiens

<400> 46

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<210> 47

<211> 1444

<212> DNA

<213> Homo sapiens

<400> 47

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<210> 48

<211> 929

<212> DNA

<213> Homo sapiens

<400> 48

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<210> 49

<211> 1676

<212> DNA

<213> Homo sapiens

<400> 49

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<210> 50

<211> 565

<212> DNA

<213> Homo sapiens

<400> 50

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<210> 51

<211> 2414

<212> DNA

<213> Homo sapiens

<400> 51

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<210> 52

<211> 1241

<212> DNA

<213> Homo sapiens

<400> 52

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 <211> 1109
 <212> DNA
 <213> Homo sapiens

<400> 53
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<400> 55

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<210> 56

<211> 1919

<212> DNA

<213> Homo sapiens

<400> 56

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<211> 1919

<212> DNA

<213> Homo sapiens

<400> 57

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<212> DNA

<213> Homo sapiens

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<211> 2482

<212> DNA

<213> Homo sapiens

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<211> 1815

<212> DNA

<213> Homo sapiens

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<210> 66

<211> 1475

<212> DNA

<213> Homo sapiens

<400> 66

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<210> 67

<211> 261

<212> DNA

<213> Homo sapiens

<400> 67

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tccctctctc cccgttctcg ccccgcccc acccctgctt cccactaccc tttgtctctt 180
gctctttctt gggcttctgt acaactcaac ttgtatacac tgtgtacaca caaccagcca 240
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<210> 68

<211> 942

<212> DNA

<213> Homo sapiens

<400> 68

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<210> 69

<211> 1027

<212> DNA

<213> Homo sapiens

<400> 69

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<210> 70

<211> 668

<212> DNA

<213> Homo sapiens

<400> 70

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<210> 71

<211> 957

<212> DNA

<213> Homo sapiens

<400> 71

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<210> 72

<211> 2201

<212> DNA

<213> Homo sapiens

<400> 72

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<210> 73

<211> 2211

<212> DNA

<213> Homo sapiens

<400> 73

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<210> 74

<211> 4087

<212> DNA

<213> Homo sapiens

<400> 74

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<213> Homo sapiens

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<211> 2353

<212> DNA

<213> Homo sapiens

<400> 77

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 <211> 1327
 <212> DNA
 <213> Homo sapiens

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<210> 83

<211> 1327

<212> DNA

<213> Homo sapiens

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<210> 84

<211> 1922

<212> DNA

<213> Homo sapiens

<400> 84

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<210> 85

<211> 1432

<212> DNA

<213> Homo sapiens

<400> 85

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<210> 86

<211> 1662

<212> DNA

<213> Homo sapiens

<400> 86

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<210> 87

<211> 1662

<212> DNA

<213> Homo sapiens

<400> 87

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1662

<210> 88

<211> 568

<212> DNA

<213> Homo sapiens

<400> 88

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<211> 1091

<212> DNA

<213> Homo sapiens

<400> 89

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<210> 90

<211> 1644

<212> DNA

<213> Homo sapiens

<400> 90

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<210> 91

<211> 1926

<212> DNA

<213> Homo sapiens

<400> 91

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<210> 92

<211> 598

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 93

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<211> 2144

<212> DNA

<213> Homo sapiens

<400> 94

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<211> 420

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<211> 1548

<212> DNA

<213> Homo sapiens

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<211> 3928

<212> DNA

<213> Homo sapiens

<400> 98

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<212> DNA

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<211> 1651

<212> DNA

<213> Homo sapiens

<400> 105

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<211> 1832

<212> DNA

<213> Homo sapiens

<400> 106

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<211> 3089

<212> DNA

<213> Homo sapiens

<400> 107

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<211> 2863

<212> DNA

<213> Homo sapiens

<400> 108

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 3112

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 2782

<212> DNA

<213> Homo sapiens

<400> 115

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<210> 116

<211> 1266

<212> DNA

<213> Homo sapiens

<400> 116

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<210> 117

<211> 716

<212> DNA

<213> Homo sapiens

<400> 117

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<210> 118

<211> 4598

<212> DNA

<213> Homo sapiens

<400> 118

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<211> 637

<212> DNA

<213> Homo sapiens

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<211> 1642

<212> DNA

<213> Homo sapiens

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<211> 1000

<212> DNA

<213> Homo sapiens

<400> 121

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<210> 122

<211> 1355

<212> DNA

<213> Homo sapiens

<400> 122

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<210> 123

<211> 363

<212> DNA

<213> Homo sapiens

<400> 123

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<210> 124

<211> 3429

<212> DNA

<213> Homo sapiens

<400> 124

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<210> 125

<211> 1129

<212> DNA

<213> Homo sapiens

<400> 125

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<210> 126

<211> 1988

<212> DNA

<213> Homo sapiens

<400> 126

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<210> 127

<211> 1867

<212> DNA

<213> Homo sapiens

<400> 127

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<210> 128

<211> 4802

<212> DNA

<213> Homo sapiens

<400> 128

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<213> Homo sapiens

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<210> 134

<211> 2125

<212> DNA

<213> Homo sapiens

<400> 134

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<210> 135

<211> 1815

<212> DNA

<213> Homo sapiens

<400> 135

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<210> 136

<211> 755

<212> DNA

<213> Homo sapiens

<400> 136

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<210> 137

<211> 3039

<212> DNA

<213> Homo sapiens

<400> 137

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<210> 138

<211> 575

<212> DNA

<213> Homo sapiens

<400> 138

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<210> 139

<211> 1794

<212> DNA

<213> Homo sapiens

<400> 139

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<210> 140

<211> 691

<212> DNA

<213> Homo sapiens

<400> 140

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<210> 141

<211> 1570

<212> DNA

<213> Homo sapiens

<400> 141

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2702

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 146

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<210> 147

<211> 2436

<212> DNA

<213> Homo sapiens

<400> 147

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<210> 148

<211> 884

<212> DNA

<213> Homo sapiens

<400> 148

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<210> 149

<211> 2872

<212> DNA

<213> Homo sapiens

<400> 149

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<210> 150

<211> 1253

<212> DNA

<213> Homo sapiens

<400> 150

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<210> 151

<211> 1444

<212> DNA

<213> Homo sapiens

<400> 151

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<211> 619

<212> DNA

<213> Homo sapiens

<400> 152

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<210> 153

<211> 1728

<212> DNA

<213> Homo sapiens

<400> 153

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<210> 154

<211> 1264

<212> DNA

<213> Homo sapiens

<400> 154

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<212> DNA

<213> Homo sapiens

<400> 155

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<210> 156

<211> 3220

<212> DNA

<213> Homo sapiens

<400> 156

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<210> 157

<211> 391

<212> DNA

<213> Homo sapiens

<400> 157

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<210> 158

<211> 4720

<212> DNA

<213> Homo sapiens

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<210> 159

<211> 779

<212> DNA

<213> Homo sapiens

<400> 159

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<211> 3655

<212> DNA

<213> Homo sapiens

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<400> 165

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<212> DNA

<213> Homo sapiens

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<211> 1359

<212> DNA

<213> Homo sapiens

<400> 167

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<211> 2961

<212> DNA

<213> Homo sapiens

<400> 168

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<211> 2162

<212> DNA

<213> Homo sapiens

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<211> 1613

<212> DNA

<213> Homo sapiens

<400> 170

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<210> 171

<211> 4160

<212> DNA

<213> Homo sapiens

<400> 171

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<210> 172

<211> 1185

<212> DNA

<213> Homo sapiens

<400> 172

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<210> 173

<211> 1293

<212> DNA

<213> Homo sapiens

<400> 173

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1293

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<210> 174

<211> 956

<212> DNA

<213> Homo sapiens

<400> 174

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<210> 175

<211> 348

<212> DNA

<213> Homo sapiens

<400> 175

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<210> 176

<211> 1019

<212> DNA

<213> Homo sapiens

<400> 176

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<210> 177

<211> 1651

<212> DNA

<213> Homo sapiens

<400> 177

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<210> 178

<211> 2701

<212> DNA

<213> Homo sapiens

<400> 178

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2701

<210> 179

<211> 1916

<212> DNA

<213> Mus musculus

<400> 179

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<210> 180

<211> 3720

<212> DNA

<213> Homo sapiens

<400> 180

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<210> 181

<211> 680

<212> DNA

<213> Mus musculus

<400> 181

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<210> 182

<211> 1849

<212> DNA

<213> Mus musculus

<400> 182

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<210> 183

<211> 466

<212> DNA

<213> Homo sapiens

<400> 183

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<210> 184

<211> 744

<212> DNA

<213> Homo sapiens

<400> 184

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<211> 1203

<212> DNA

<213> Homo sapiens

<400> 185

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<210> 186

<211> 883

<212> DNA

<213> Homo sapiens

<400> 186

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<210> 187

<211> 1009

<212> DNA

<213> Homo sapiens

<400> 187

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<210> 188

<211> 1874

<212> DNA

<213> Homo sapiens

<400> 188

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<210> 189

<211> 1114

<212> DNA

<213> Homo sapiens

<400> 189

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<210> 190

<211> 1756

<212> DNA

<213> Homo sapiens

<400> 190

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<210> 191

<211> 2071

<212> DNA

<213> Homo sapiens

<400> 191

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<210> 192

<211> 310

<212> DNA

<213> Homo sapiens

<400> 192

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tactgatcat cttctttgaa gaaacatgaa gttacactat gttgctgtgc ttactctagc 180
catcctgatg ttctgacat ggcttcacga atcactgagc tgtaacaaag cactctgtgc 240
tagtgatgtg agcaaatgcc tcattcagga gctctgccag tgccggccgg gacgattgaa 300
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<210> 193

<211> 971

<212> DNA

<213> Homo sapiens

<400> 193

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gaagtggcaa caacactcgc tgcctgcagcc tgtatgctcc aggcaaggag gactgtccaa 180
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<210> 194

<211> 1699

<212> DNA

<213> Homo sapiens

<400> 194

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aatgaggagt caacgctcag ggacattcta ggtctttaca ggtcagacag aagagaggtt 540

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<210> 195

<211> 2902

<212> DNA

<213> Homo sapiens

<400> 195

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<210> 196

<211> 3134

<212> DNA

<213> Homo sapiens

<400> 196

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<211> 3323

<212> DNA

<213> Homo sapiens

<400> 197

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<211> 1225

<212> DNA

<213> Homo sapiens

<400> 198

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<211> 2671

<212> DNA

<213> Homo sapiens

<400> 199

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<210> 200

<211> 1942

<212> DNA

<213> Homo sapiens

<400> 200

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<210> 201

<211> 628

<212> DNA

<213> Homo sapiens

<400> 201

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<210> 202

<211> 1877

<212> DNA

<213> Homo sapiens

<400> 202

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<211> 2340
<212> DNA
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<400> 203

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<212> DNA
<213> Homo sapiens

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<211> 1887

<212> DNA

<213> Homo sapiens

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<211> 876

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1439

<212> DNA

<213> Homo sapiens

<400> 208

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<210> 209

<211> 2888

<212> DNA

<213> Homo sapiens

<400> 209

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<213> Homo sapiens

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<210> 212

<211> 1175

<212> DNA

<213> Homo sapiens

<400> 212

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<212> DNA

<213> Homo sapiens

<400> 214

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<211> 1847

<212> DNA

<213> Homo sapiens

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<211> 1070

<212> DNA

<213> Homo sapiens

<400> 216

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<211> 1897

<212> DNA

<213> Homo sapiens

<400> 217

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<210> 218

<211> 2099

<212> DNA

<213> Homo sapiens

<400> 218

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<210> 219

<211> 2666

<212> DNA

<213> Homo sapiens

<400> 219

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<210> 220

<211> 2028

<212> DNA

<213> Homo sapiens

<400> 220

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 <212> DNA
 <213> Homo sapiens

<400> 221
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 <211> 1109
 <212> DNA
 <213> Homo sapiens

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 <213> Homo sapiens

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<210> 224

<211> 1074

<212> DNA

<213> Homo sapiens

<400> 224

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<211> 2139

<212> DNA

<213> Homo sapiens

<400> 225

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<210> 226

<211> 983

<212> DNA

<213> Homo sapiens

<400> 226

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<210> 227

<211> 2438

<212> DNA

<213> Homo sapiens

<400> 227

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<210> 228

<211> 1510

<212> DNA

<213> Homo sapiens

<400> 228

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 <211> 1186
 <212> DNA
 <213> Homo sapiens

<400> 229
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 <211> 1057
 <212> DNA
 <213> Homo sapiens

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<210> 231
 <211> 1900
 <212> DNA
 <213> Homo sapiens

<400> 231
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<210> 232

<211> 943

<212> DNA

<213> Homo sapiens

<400> 232

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<210> 233

<211> 1974

<212> DNA

<213> Homo sapiens

<400> 233

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<211> 731

<212> DNA

<213> Homo sapiens

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<211> 919

<212> DNA

<213> Homo sapiens

<400> 235

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<211> 1348

<212> DNA

<213> Homo sapiens

<400> 236

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<211> 2311

<212> DNA

<213> Homo sapiens

<400> 237

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 3634

<212> DNA

<213> Homo sapiens

<400> 242

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<211> 2405

<212> DNA

<213> Homo sapiens

<400> 243

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<211> 1747

<212> DNA

<213> Homo sapiens

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<211> 1198

<212> DNA

<213> Homo sapiens

<400> 245

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<211> 1146

<212> DNA

<213> Homo sapiens

<400> 246

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<210> 259

<211> 1969

<212> DNA

<213> Homo sapiens

<400> 259

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<210> 260

<211> 2581

<212> DNA

<213> Homo sapiens

<400> 260

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<210> 261

<211> 2500

<212> DNA

<213> Homo sapiens

<400> 261

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<210> 262

<211> 815

<212> DNA

<213> Homo sapiens

<400> 262

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<210> 263

<211> 1946

<212> DNA

<213> Homo sapiens

<400> 263

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<210> 264

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 264

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<211> 3004

<212> DNA

<213> Homo sapiens

<400> 265

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<210> 266

<211> 1863

<212> DNA

<213> Homo sapiens

<400> 266

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<210> 267

<211> 2341

<212> DNA

<213> Homo sapiens

<400> 267

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<210> 268

<211> 507

<212> DNA

<213> Homo sapiens

<400> 268

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<211> 2472

<212> DNA

<213> Homo sapiens

<400> 269

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<210> 270

<211> 2854

<212> DNA

<213> Homo sapiens

<400> 270

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<210> 271

<211> 2528

<212> DNA

<213> Homo sapiens

<400> 271

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<210> 272

<211> 3427

<212> DNA

<213> Homo sapiens

<400> 272

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<210> 273

<211> 3355

<212> DNA

<213> Homo sapiens

<400> 273

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<210> 274

<211> 1339

<212> DNA

<213> Homo sapiens

<400> 274

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<210> 275

<211> 638

<212> DNA

<213> Homo sapiens

<400> 275

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<210> 276

<211> 2584

<212> DNA

<213> Homo sapiens

<400> 276

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<212> DNA

<213> Homo sapiens

<400> 277


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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

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<210> 284

<211> 1472

<212> DNA

<213> Homo sapiens

<400> 284

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<210> 285

<211> 564

<212> DNA

<213> Homo sapiens

<400> 285

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gcacaatata aggcctccac agtgacacaa ggatctcata ataaagcctg taccatgctt 360
tttatgatac tctatttttt tactatggct ggcagtgtat ggtgggtaat tcttaccatc 420

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acatggtttt tagcagctgt gccaaagtgg ggtagtgaag ctattgagaa gaaagcattg 480
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aataaaaattg aaggtgacaa tatt 564

<210> 286
<211> 695
<212> DNA
<213> Homo sapiens

<400> 286
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taagaatatc aagtattttct ctggctcttg acagaaaaaa atcagttgac ttaacccttt 180
gctgtcaaaa gagttggcgt ttcctgttct ggtgtctact gccaaacgtt atggtactta 240
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tcaaaagggtc ttgctgctgt caggtgttat gcactccatc catcataact gtatgaaaca 660
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<210> 287
<211> 694
<212> DNA
<213> Homo sapiens

<400> 287
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aatgcaataa atagaaaaat gtggtttaca aaat 694

<210> 288
<211> 1393
<212> DNA
<213> Homo sapiens

<400> 288
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gaactcaaat ctccaaattc tggcatcgga cttacaacac tagttagaag ctaataaaca 180
ttaaggaatt tccaagggga atcttaacta agtctcaatc ttactgacca gattaccac 240
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<210> 289

<211> 1733

<212> DNA

<213> Homo sapiens

<400> 289

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ttaagtacag tgataaagca tctatatctt gtaaaaaaaa aaaaaatctg cctatgcatg 240
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ttaaggtttt taacataagc ttgtcaatgc acatgtatag ggtagcatg tttagcaaac 480
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<210> 290

<211> 2195

<212> DNA

<213> Homo sapiens

<400> 290

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ggaggagagg agaggccggc ccgctgcga aaaaagcaaat ggatttccac ctgacaaatc 180
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<210> 291
 <211> 305
 <212> DNA
 <213> Homo sapiens

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<400> 291
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tgtaaatattc aaaactgtga attgggttgc caaaaactgt tgcccttcgt tagatgcttc 180
aaacagtgtta aatcctatac tgcacctgt ccacctctgc tccctcctcc ctcccctgag 240
agtgaggacc tcatccgacc atgtaattac cattcgcttg ctattaaaga gccttttcaa 300
ctctg 305

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<210> 292
 <211> 819
 <212> DNA
 <213> Homo sapiens

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<400> 292
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<210> 293
 <211> 1057

<212> DNA

<213> Homo sapiens

<400> 293

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tactagcatt acaggctgag gaaatcttgg tatggtgatg atttttactc tagtgacagc 480
tgtgcaagaa aaattaaatg aaatagtaga tcagataaaa actagaagag aagaagaaaa 540
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```

<210> 294

<211> 1794

<212> DNA

<213> Homo sapiens

<400> 294

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<210> 295

<211> 447

<212> DNA

<213> Homo sapiens

<400> 295

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<212> DNA

<213> Homo sapiens

<400> 296

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<210> 297

<211> 2512

<212> DNA

<213> Homo sapiens

<400> 297

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<211> 1107

<212> DNA

<213> Homo sapiens

<400> 298

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<211> 1051

<212> DNA

<213> Homo sapiens

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<211> 1669

<212> DNA

<213> Homo sapiens

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<211> 2154

<212> DNA

<213> Homo sapiens

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<210> 302

<211> 5770

<212> DNA

<213> Homo sapiens

<400> 302

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<210> 303

<211> 798

<212> DNA

<213> Homo sapiens

<400> 303

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798

<210> 304

<211> 1279

<212> DNA

<213> Homo sapiens

<400> 304

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1279

<210> 305

<211> 1398

<212> DNA

<213> Homo sapiens

<400> 305

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<210> 306

<211> 896

<212> DNA

<213> Homo sapiens

<400> 306

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<210> 307

<211> 2232

<212> DNA

<213> Homo sapiens

<400> 307

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<210> 308

<211> 654

<212> DNA

<213> Homo sapiens

<400> 308

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<210> 309

<211> 610

<212> DNA

<213> Homo sapiens

<400> 309

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<210> 310

<211> 1064

<212> DNA

<213> Homo sapiens

<400> 310

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<210> 311

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 311

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<210> 312

<211> 1354

<212> DNA

<213> Homo sapiens

<400> 312

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 <211> 994
 <212> DNA
 <213> Homo sapiens

<400> 313
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<210> 314
 <211> 795
 <212> DNA
 <213> Homo sapiens

<400> 314
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 <211> 1526
 <212> DNA
 <213> Homo sapiens

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 aaaatttggg tcttagtaac ctaatgtagt tacttacttc ttttatccta ctacatatat 180
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<210> 316

<211> 1354

<212> DNA

<213> Homo sapiens

<400> 316

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<210> 317

<211> 1316

<212> DNA

<213> Homo sapiens

<400> 317

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<210> 318

<211> 787

<212> DNA

<213> Homo sapiens

<400> 318

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<210> 319

<211> 2804

<212> DNA

<213> Homo sapiens

<400> 319

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<210> 320

<211> 1604

<212> DNA

<213> Homo sapiens

<400> 320

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<210> 321

<211> 2425

<212> DNA

<213> Homo sapiens

<400> 321

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<211> 1558

<212> DNA

<213> Homo sapiens

<400> 322

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<210> 323

<211> 975

<212> DNA

<213> Homo sapiens

<400> 323

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<210> 324

<211> 1782

<212> DNA

<213> Homo sapiens

<400> 324

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<210> 325
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 <212> DNA
 <213> Homo sapiens

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<400> 325
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 <211> 1695
 <212> DNA
 <213> Homo sapiens

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<210> 327

<211> 2067

<212> DNA

<213> Homo sapiens

<400> 327

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10232

its SEQ ID NOs: 1-623.

The special technical feature of each protein molecule is considered to be the structure as determined by its amino acid sequence encoded by the polynucleotides of SEQ ID NOs: 1-623.

The antibody specific to the proteins of the invention has a special technical feature with respect to its structure and physicochemical properties.

Additionally the claimed methods do not share the same technical feature as set forth above and they lack unity of invention because methods are alternate methods of use.

Accordingly, Groups 1-6853 are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept and so lack unity of invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10232

If group 2494 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 3116-3738, claim 14, in part, drawn to the special technical feature of a method of identifying a compound that modulates the activity of the protein by monitoring the effect of the test compound on the activity of the protein, wherein the protein is encoded by the polynucleotides of SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 14 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 3116 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 3117 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 3739-4361, claim 15, in part, drawn to the special technical feature of a method of identifying a compound that modulates the expression of the polynucleotide by monitoring the effect of the test compound on the expression of the polynucleotide, wherein polynucleotide is set forth in SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 15 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 3739 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 3740 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 4362-4984, claim 16, in part, drawn to the special technical feature of a method of identifying a compound that modulates the production of the protein by monitoring the effect of the test compound on the production of the protein, wherein the protein is encoded by the polynucleotides of SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 16 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 4362 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 4363 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 4985-5607, claim 17, in part, drawn to the special technical feature of a method for treating a disorder characterized by aberrant expression of the polynucleotide by administering a compound that modulates expression of the polypeptide, wherein polynucleotide is set forth in SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 17 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 4985 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 4986 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 5608-6230, claim 18, in part, drawn to the special technical feature of a method for treating a disorder characterized by aberrant production of the protein by administering a compound that modulates production of the protein, wherein the protein is encoded by the polynucleotides set forth in SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 18 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 5608 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 5609 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 6231-6853, claim 19, in part, drawn to the special technical feature of a method for treating a disorder characterized by aberrant activity of the protein by administering a compound that modulates activity of the protein, wherein the protein is encoded by the polynucleotides set forth in SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 19 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 6231 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 6232 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

The inventions listed as Groups 1-6853 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-6853 appears to be that they all relate to a polynucleotide. However it is apparent that SIGMA Catalog, 1999, page 1610 discloses a primer with poly T, wherein said primer renders claim 3 among others not novel (see SEQ ID NO: 143, poly A; and SEQ ID NO: 521, poly T), because poly T primer is capable to hybridize to SEQ ID NO: 143 and to a complement of SEQ ID NO: 521. This technical feature does not constitute a special technical feature as it does not define a contribution over the prior art.

The nucleic acids and proteins of each of the invention do not share the same or corresponding special technical feature with each other. The special technical feature of each DNA molecule is considered to be the structure as determined by

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/10232

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

C07H 21/02, 21/04; C07K 5/00, 14/00; C12Q 1/68; C12P 21/06; C12N 1/20; C12N 15/63; C12N 5/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

536/23.1, 23.5, 24.31; 530/300.350; 435/6, 69.1, 252.3, 320.1, 325

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

Sequence search (Database: GenEmbl, N_Geneseq_0601, EST, Issued_Patents_NA)

EAST (Database: USPAT, DERWENT, EPO, JPO)

STN (Database: Biosis, Caplus, Embase, Medline, Scisearch)

Search Terms: polynucleotides, DNA, nucleic acid, secreted proteins

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-623, claims 1-7, all in part, drawn to the special technical feature of an isolated nucleic acid of SEQ ID NO 1-623, vector, host cell and process for producing protein, wherein values of SEQ IDs 1-623 of claim 1 correspond to values of SEQ ID NO: 1-623 of claims 2 and 3. For examples,

Group 1 is the main invention and this correlates to SEQ ID NO: 1 of claims 1-3.

If group 2 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 624-1246, claim 8, in part, drawn to the special technical feature of a protein encoded by the polynucleotides of SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 8 correspond to values of SEQ ID NO: 1-623 of claims 1-3. For examples,

If group 624 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 625 is elected, this correlates to SEQ ID NO: 2

of claims 1-3.

Groups 1247-1869, claim 9, in part, drawn to the special technical feature of an isolated antibody which binds to a protein encoded by the polynucleotides of SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 9 correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 1247 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 1248 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 1870-2492, claims 10, in part, drawn to the special technical feature of a method of detecting a protein in a biological sample by determining the binding of the protein by a specific antibody, wherein the protein is encoded by the polynucleotides of SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 10, correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 1870 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

If group 1871 is elected, this correlates to SEQ ID NO: 2 of claims 1-3.

Groups 2493-3115, claim 11, in part, drawn to the special technical feature of a method of detecting a polynucleotide in a biological sample by determining the hybridization of the polynucleotide by a polynucleotide reagent, wherein the polynucleotide is set forth in SEQ ID NO: 1-623, wherein values of SEQ IDs 1-623 of claim 11, correspond to values of SEQ ID NO: 1-623 of claims 1, 2 and 3. For examples,

If group 2493 is elected, this correlates to SEQ ID NO: 1 of claims 1-3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10232

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 12-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
claims 1-7, all in part (SEQ ID NO:1)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/10232

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.5, 24.31; 530/300,350; 435/6, 69.1, 252.3, 320.1, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	Database: GenEmbl; Accession NO: AF212241; Li et al. "A novel gene expressed in human pheochromocytoma"; 02 March 2001; having 99.9% sequence identity to SEQ ID NO: 1; see entire document.	1-4
X, P	Database: N_Geneseq_0601; Accession NO: AAF63730; Xiao et al.; "Human helf3-iso encoding nucleotide sequence SEQ ID NO: 6"; 11 October 2000; having 94.5% sequence identity to SEQ ID NO:1; methods for the preparation of helf3iso protein; see entire document.	1-4, 7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

04 NOVEMBER 2001

Date of mailing of the international search report

28 DEC 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
RITA MITRA

Telephone No. (703) 308-0196

PCT/ISA/210 (second sheet) (July 1998) *

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 October 2001 (18.10.2001)

PCT

(10) International Publication Number
WO 01/77289 A3

(51) International Patent Classification⁷: C07H 21/02,
21/04, C07K 5/00, 14/00, C12Q 1/68, C12P 21/06, C12N
1/20, 15/63, 5/00

(21) International Application Number: PCT/US01/10232

(22) International Filing Date: 29 March 2001 (29.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/195,605 6 April 2000 (06.04.2000) US

(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87
Cambridge Park Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02460 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVAL-LIE, Edward, R.; 113 Ann Lee Road, Harvard, MA 01452 (US). COLLINS-RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). EVANS, Cheryl; 19236 Golden Meadow Drive, Germantown, MD 20876 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 38 Clarinda Park East, Dun Laoghaire, County Dublin (IE). AGOSTINO, Michael, J.; 26 Walcott Avenue, Andover, MA 01810 (US). BOWMAN, Michael, R.; 63 Gloucester Road, Westwood, MA (US). SPAULDING, Vikki; 47C Beatrice Street, Danville, NH (US). WONG, Gordon, G.; 239 Clark Road, Brookline, MA 02146 (US). CLARK, Hilary, F.; 495 Harkness Avenue, San Francisco, CA 94134 (US).

FECHTEL, Kim; 46 Marion Road, Arlington, MA 02174 (US). HOWES, Steven, H.; 37 Yerca Road #2, No. 2, Cambridge, MA 02140 (US). RESNICK, Richard, J.; 36 Burnside Avenue, Somerville, MA 02144 (US). GULUKOTA, Kamalakur; 3 Stout Court, Lawrenceville, NJ 08648 (US). GRAHAM, James, R.; 40 Peirce Street, Arlington, MA 02476 (US).

(74) Agents: MANDRAGOURAS, Amy, E. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
21 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

(57) Abstract: Isolated polynucleotides which have been derived from a variety of human tissue sources, and which encode novel secreted proteins, are provided. Also provided are methods for producing proteins using these polynucleotides, and the proteins so produced.

WO 01/77289 A3

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<220>

<223> linker sequence

<400> 625

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<210> 626

<211> 8

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<220>

<221> unsure

<222> (7)..(8)

<400> 626

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<210> 627

<211> 15

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<220>

<221> unsure

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557

<210> 620

<211> 728

<212> DNA

<213> Homo sapiens

<400> 620

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tttaccocct tcaccttcca gggacgcagt tgttttgagg ttagacgtgg cagctctgtg 660
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tctcctag 728

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<210> 621

<211> 753

<212> DNA

<213> Homo sapiens

<400> 621

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gcattggtcc gtggtgggag tgaagctgct cccacaagat gcattcccaa ctggatcagg 180
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<210> 622

<211> 685

<212> DNA

<213> Homo sapiens

<400> 622

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aacacccttg ctgtgccctt taatgggatt gaaagcactt ttaccacatg gagaaatata 540
tttttaattt gtgatgcttt tctacaaggc ccactatctc tgagtttaat gtgtttccaa 600
cacttaagga gactctaag aaagctgatg aattttcttt tctgtccaaa caagtaaaat 660
aaaaataaaa gtctatttag atgtc 685

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<210> 623

<211> 596

<210> 616
<211> 445
<212> DNA
<213> Homo sapiens

<400> 616
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ctcaggtttag accctgggcc ctggagctta ggggattctc cccacccag cccacacct 360
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aaataaaaaa caacactttt gcatg 445

<210> 617
<211> 394
<212> DNA
<213> Homo sapiens

<400> 617
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gcggggcgcc ggcgccgngg gggcgccct gggg 394

<210> 618
<211> 710
<212> DNA
<213> Homo sapiens

<400> 618
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tgggggtggc ccactgccct cccctggccc tcatgtcccc ccggggctgg ggtccgcctg 660
cctgtgctgt gcttgcgacg tgcatcaata aaccaccatg gcctgagggc 710

<210> 619
<211> 557
<212> DNA
<213> Homo sapiens

<400> 619
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aataaaaaa aagtgaatt tgggacaata gggaaataaa gtagaaatta tacctggatt 420
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agggcagctc tgtgcgatgc taaaaggggc agtaagccat ggcttcata atacaagaaa 540

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tgcacccgcc cccaaccccg gccttccaga ctcagcaaca gactcactcc ccctcccggc 420
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cggccagcat caccaagggc acgccagcca cctaagaacc gccctgcca gccaccacc 600
ccaccacccc tcccaccacc cagcctggct gctccactgt cccgggctgc cctggctggg 660
ggcccggtgca ccccggcagg tggaccagcc tcagccttgg cacctgggca ccca 714

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<210> 613

<211> 531

<212> DNA

<213> Homo sapiens

<400> 613

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gttctcagca ccgctcactg ctgccgggca cactgggacc agcaggctcc tcagccaacc 120
ctgtccctcg gcccgccctt gccagagagg gaccccagca catcgtgggc acgggcaggg 180
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tgacacagag actatcttat caattgtcag tccggttcct ttaccatagg attctccaca 480
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<210> 614

<211> 907

<212> DNA

<213> Homo sapiens

<400> 614

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cttctctttt atttattttg ttctccattt gtggccctca cctccgcctg ccttcccttc 180
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cggggca 907

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<210> 615

<211> 543

<212> DNA

<213> Homo sapiens

<400> 615

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gtactggtct catggtttta gacctggcac ccagtgggta tggggagccc tgggcacctg 180
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ggaggatcgc ttgagaacag gagtttgaga ccagcctggg caacatagtg agactccacc 540
tct 543

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gtatgggccc ctgtgacaaa acacctaaga ctgggtagtt tataaagaac agacattcag 480
gcnaggcacg gtgactcacg cctgtaatcc cagcactttg ggaggccgag gcgcgtggat 540
catttgaggt caggagtttg aaaccagcct ggccaacatg gtgaaacccc atctctacta 600
aaaaaaca aaactagctggg ggtggtggtg catgcctgtg gtcccagcta cttgggaggg 660
taaggtagaa gaattgcttg aacctgggag gcagagattg cagtggagccg agatcacgcc 720
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<210> 609

<211> 476

<212> DNA

<213> Homo sapiens

<400> 609

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acctggtcca tctccatgat cacttaccta aactagtgtg gttgcctcct gtggggttcc 180
cagcttccac cctcaccccc tacgacttct tgtccagaca gcagccagaa tggctcctgta 240
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ggaggccgag gtgggcatga gccaccacgc ccagccatat attttcaaaa ttagccaggc 420
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<210> 610

<211> 406

<212> DNA

<213> Homo sapiens

<400> 610

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caccttctgg gctcctggcc agcacccac ccccaggagc cagggacagg tggcatgtgt 60
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agcccagaca tcaagaactt ctgatctcct gccaccagg aggggactta gccatggact 180
tggccagtag gcctggggag ggagggtttt ggcagccaaa gtccactggc cctgccgtgc 240
ccctgagtag gaaactgtcc cctaggggct ggggtggccc actgatatat gcaaaccgcg 300
cggtcggagc cctgttctct cctgtgtctc tctgtgcccc ggctgggtct cccccaaccc 360
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<210> 611

<211> 433

<212> DNA

<213> Homo sapiens

<400> 611

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agtgtacctt ctggtgcaga atacatttag atataaaaag acgttattaa tacattgcac 120
agttttcaaa atttaaaaac aaaaccgaac gctgctctgc ggagccgcc gccgggttgc 180
tgctacatga acggtccag ccgaggccca gcgccttcc aacgtccgct gccccggcag 240
gttccctcgg ggtcttttgg gctctaaatt ggctcaccgc agcctcttgc gcggggtctg 300
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acgacttctc aggcgctgat ctcttgctt tggcgaagaa atcggagatc agaggcccg 420
nacagcttct tga 433

```

<210> 612

<211> 714

<212> DNA

<213> Homo sapiens

<400> 612

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gttttttgtg tttttggaag agatgggtgt tcaactgtgt ggccaggatg gtctcgatct 60
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accgcgcccc gccggaactc tgtttcaaaa agaaaaaaa caaaggaaaa agagggtgtc 180
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gccatgggtg gcttctgtgt gctgtcaca gcttgggagg gagaagcagg cactccatc 300
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<210> 605
 <211> 886
 <212> DNA
 <213> Homo sapiens

<400> 605
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<210> 606
 <211> 361
 <212> DNA
 <213> Homo sapiens

<400> 606
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 g 361

<210> 607
 <211> 455
 <212> DNA
 <213> Homo sapiens

<400> 607
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 tcttgggcag cggcctttcc tccgggtccg ggtta 455

<210> 608
 <211> 760
 <212> DNA
 <213> Homo sapiens

<400> 608
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 gatgacgtgc ccaagtgac gcaactcgtg aacagccgtg cctgccttgg gcgcagctc 360
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<210> 602
 <211> 579
 <212> DNA
 <213> Homo sapiens

<400> 602
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<210> 603
 <211> 1358
 <212> DNA
 <213> Homo sapiens

<400> 603
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 gtgctggaga tgcctgaaggc cggcgtgaag gacacggaaa accgcgtggc cctccatgcc 240
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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1258

<212> DNA

<213> Homo sapiens

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<212> DNA

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<212> DNA

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<211> 3615

<212> DNA

<213> Homo sapiens

<400> 596

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<213> Homo sapiens

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<211> 1379

<212> DNA

<213> Homo sapiens

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<210> 587

<211> 935

<212> DNA

<213> Homo sapiens

<400> 587

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<210> 584

<211> 1657

<212> DNA

<213> Homo sapiens

<400> 584

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<210> 585

<211> 602

<212> DNA

<213> Homo sapiens

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1521

<210> 581

<211> 969

<212> DNA

<213> Homo sapiens

<400> 581

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<211> 1241

<212> DNA

<213> Homo sapiens

<400> 582

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<210> 583

<211> 1496

<212> DNA

<213> Homo sapiens

<400> 583

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<211> 1536
<212> DNA
<213> Homo sapiens

<400> 579
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<210> 580
<211> 1521
<212> DNA
<213> Homo sapiens

<400> 580
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<210> 577

<211> 1055

<212> DNA

<213> Homo sapiens

<400> 577

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<210> 578

<211> 929

<212> DNA

<213> Homo sapiens

<400> 578

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<210> 579


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<211> 1222

<212> DNA

<213> Homo sapiens

<400> 575

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<211> 1348

<212> DNA

<213> Homo sapiens

<400> 576

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 <211> 1902
 <212> DNA
 <213> Homo sapiens

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<210> 571

<211> 1414

<212> DNA

<213> Homo sapiens

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<211> 1031

<212> DNA

<213> Homo sapiens

<400> 572

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<211> 1928

<212> DNA

<213> Homo sapiens

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<210> 568

<211> 1220

<212> DNA

<213> Homo sapiens

<400> 568

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<210> 569

<211> 2515

<212> DNA

<213> Homo sapiens

<400> 569

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<213> Homo sapiens

<400> 565

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<210> 566

<211> 1216

<212> DNA

<213> Homo sapiens

<400> 566

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```

<210> 567

<211> 1203

<212> DNA

<213> Homo sapiens

<400> 567

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ctggggctgc taaggaaagta attaggtta catgaagtca tgggtgggct ctgatctgct 240
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<400> 563

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<210> 564

<211> 1312

<212> DNA

<213> Homo sapiens

<400> 564

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```

<210> 565

<211> 1142

<212> DNA

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```

<210> 560

<211> 469

<212> DNA

<213> Homo sapiens

<400> 560

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aacagtaaca cgatgttcat ttacaagcgg cttatgttct atttcccaca atctttttta 420
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```

<210> 561

<211> 685

<212> DNA

<213> Homo sapiens

<400> 561

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tgactttcga agttttttta acctctgaat tggtagacat ttaaaatttc aagtgtactt 660
taaaataaaa tacttctaata ggaac                                           685

```

<210> 562

<211> 505

<212> DNA

<213> Homo sapiens

<400> 562

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catagtggaa gtgagctaca acgtagtagc tgcgtgttag tacgatgtct agtgatgagt 480
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```

<210> 563

<211> 1722

<212> DNA

<213> Homo sapiens

<213> Homo sapiens

<400> 557

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```

<210> 558

<211> 530

<212> DNA

<213> Homo sapiens

<400> 558

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ccacagtggg cttccataaa tatctgtaaa atctcggaac cattgtctcg attcacacca 480
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```

<210> 559

<211> 1446

<212> DNA

<213> Homo sapiens

<400> 559

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<210> 556

<211> 3054

<212> DNA

<213> Homo sapiens

<400> 556

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<212> DNA

<213> Homo sapiens

<400> 553

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<213> Homo sapiens

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<211> 625

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 2029

<212> DNA

<213> Homo sapiens

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<210> 333

<211> 1754

<212> DNA

<213> Homo sapiens

<400> 333

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ttagattcac ttttgtgata atgccatgtt tccgttatga acaactaggt agttggagaa 180
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<210> 334

<211> 1613

<212> DNA

<213> Homo sapiens

<400> 334

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<210> 335

<211> 1733

<212> DNA

<213> Homo sapiens

<400> 335

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<210> 336

<211> 1684

<212> DNA

<213> Homo sapiens

<400> 336

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gctaacgcca agggaacttc atttttttct tcaactattat gcactttcat ggtatagtct 240
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```

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<210> 337

<211> 1288

<212> DNA

<213> Homo sapiens

<400> 337

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<210> 338

<211> 679

<212> DNA

<213> Homo sapiens

<400> 338

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```

<210> 339

<211> 1531

<212> DNA

<213> Homo sapiens

<400> 339

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<210> 340

<211> 1478

<212> DNA

<213> Homo sapiens

<400> 340

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<210> 341

<211> 524

<212> DNA

<213> Homo sapiens

<400> 341

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<210> 342

<211> 1823

<212> DNA

<213> Homo sapiens

<400> 342

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<210> 343

<211> 1381

<212> DNA

<213> Xenopus sp.

<400> 343

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tgcccaagag caccatttac cgtggagaga tgtgctttt tgattctgag gatcctgca 180
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tctttggcaa actggcgagt ggcagatatc tgccctcaac ttatgtggtt cgagaagacc 480
tagttgtgtg ggaggaaatt cgtgatgtta gtaaccttgg catctttatt taccaacttt 540

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gcaataacag aaagtccttc cgccttcgtc gcagagacct cttgctgggt ttcaacaaac 600
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1381

<210> 344

<211> 1554

<212> DNA

<213> *Xenopus* sp.

<400> 344

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<210> 345

<211> 1998

<212> DNA

<213> *Xenopus* sp.

<400> 345

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gatccccaac ttgctggaac atgagacgat ggccgaggca atccaacaat cctcaagctg 300
gttacctctt ttggcaagag agtgccatcc tgatgcaaga atattcctct gctcactctt 360
tgcaactatt tgccttgatc ggtatatctt cccatgtcgc agtctgtgtg aggtgtaag 420
gagcagctgt gccctatca tggcctgtta tgggtaccct tggcctgaga tctcaaatg 480

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aaaaaaaaa aactcgag

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<210> 346

<211> 1145

<212> DNA

<213> *Xenopus* sp.

<400> 346

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tgttttgcgt tgcttcttgg cgtgtggctc gcaatctatg tatctggact tctttggcag 180
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<210> 347

<211> 1140

<212> DNA

<213> *Xenopus* sp.

<400> 347

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cgtcggctac tcggagatgc ggttgccaaa cctgttggga cacactaaca tggcagaagt 180

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<210> 348

<211> 807

<212> DNA

<213> Homo sapiens

<400> 348

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cctccccagt  accttgtttt  ctgtgtcctt  gtagecgtgg  tccttcagca  tatctctgtg  180
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agaagagagg  actgtgtgcc  tttaacgaga  ggggtgctgc  ttcgtgctat  aaagccaaag  780
ccattaaaaa  aagatttctt  ttctgcc  807

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<210> 349

<211> 533

<212> DNA

<213> Homo sapiens

<400> 349

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taacattaga  aaagtgtctat  ttgccctcaa  ccaaagagag  agaaagagag  ggaataactat  180
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<210> 350

<211> 1127

<212> DNA

<213> Homo sapiens

<400> 350

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gaaaaaagga tttttttaa gaacaataac cagaaagttt gagacaattg agtattatag 1080
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<210> 351

<211> 812

<212> DNA

<213> Homo sapiens

<400> 351

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gaaataggaa cacaccagga tgagcagtat ggctaaaagc tatttattcc aaaatgaaa 720
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<210> 352

<211> 669

<212> DNA

<213> Homo sapiens

<400> 352

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cagaatgata agtgcaatag ttgtaaatct acttgacact gtaataaact gaactgaact 660
ttcaaagtc 669

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<210> 353

<211> 888

<212> DNA

<213> Homo sapiens

<400> 353

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<210> 354

<211> 1561

<212> DNA

<213> Homo sapiens

<400> 354

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<210> 355

<211> 1997

<212> DNA

<213> Homo sapiens

<400> 355

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atatcattac catatgatct aatgtgggtg tcagccggat tgtgttcatt gagggaaacc 180
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```



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gtttgtgaaaa tacatgagat aaatcatgaa gggcactatc atcctccttc tgcctgcaca 420
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ccaaacacta gctctgtatt aatccccatc attactggta aagcctcatt tgaatgtgtg 1920
aattcaaac aggcctatgta aaatttttac taatgtcatt attttgaaaa aataaattta 1980
aaaatacatt caaaatt

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<210> 356

<211> 909

<212> DNA

<213> Homo sapiens

<400> 356

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catccatcat agccaggcca ctaacttgac ttgggtgcaag agattcttgc tgcgaacttt 180
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<210> 357

<211> 1123

<212> DNA

<213> Homo sapiens

<400> 357

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tcatccccc accagaatac aatccgcgg aactgttcca ggctccgagg cctccaagct 180
gtagctatga cggcgcgagg gactccgagc cgcttcttgg ccagcgttct ccacaacgga 240
ctgggtcgct atgtgcagca gctgcagcgt ctgagcttca gcgtcagccg cgacggcgcc 300

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```

tcgtctcgcg ggcgcagggg gttcgtggag cgggagggtga tcgacttcgc ccgacggaat 360
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taccttaacg gggctgtgcg cgaggagagc atccactgca agtcggtcga ggagatctcg 480
acgctgggtgc agaagctggc cgaccagtcg ggcttggacg tgatccgcat ccgcaagccc 540
ttccacacg acaaccctag catccagggc cagtggcacc ccttcaccaa caagccgacc 600
acgttccgcg ggctacgccc ccgagaggtt caggatcctg cccagcccca ggtgcaagca 660
cagtgaagag ttgccccacc aactgcagcc ccaggctttg gactgttact ccggtaaagg 720
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<210> 358

<211> 382

<212> DNA

<213> Homo sapiens

<400> 358

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gcaaagaaga aatgttttac agactttatt cactatgtcc cattgttcta aaatgataac 180
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aaatgaaaac ctctgcactt taattttttt cagtaatttc cagctatttc taggtataaa 360
gagcagctcg tttctcttat tt 382

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<210> 359

<211> 1274

<212> DNA

<213> Homo sapiens

<400> 359

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tgaattcctt ctaactggaa catttgtgtt gtatctgtaa cactggcact gaaataaaga 1260
ccacacgggt aaag 1274

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<210> 360

<211> 571

<212> DNA

<213> Homo sapiens

<400> 360

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acagactggc aataaactcc tactaaatcc c

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<210> 361

<211> 974

<212> DNA

<213> Homo sapiens

<400> 361

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<210> 362

<211> 593

<212> DNA

<213> Homo sapiens

<400> 362

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gaacttttca aggccctagg gcttcataaa cttcacttac caaatacttc aagggtattca 180
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gtagacattt gctcatgttg gtaaatacaa tcacctatat gaaaaaattg ttttcacctg 540
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<210> 363

<211> 900

<212> DNA

<213> Homo sapiens

<400> 363

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gggttttagg tgagaaagat tgtctttgat ggtagaatag gcatctgaag ggtaagtact 120
agttataaat gttagccctg gacagatgtt aacaccagta aagtctagtt acagagtaaa 180
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tataaaactg gtaagtatta tagttgtcta ttttcocttt ttgactgaat ctaaaaaaca 780
cactttgcat gttttcacat ttataaatac ctttcttaga gcttcatact gtttcattgt 840
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```

<210> 364

<211> 349

<212> DNA

<213> Homo sapiens

<400> 364

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aaaccaaaaca atgtttccat tgttttgcac gcagaggaac cttatattga aaatgaagag 300
ccagatgacc ctctctttgc acaatagata aaagtcttta tatgaatat 349

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<210> 365

<211> 7

<212> DNA

<213> Homo sapiens

<400> 365

tagacca

7

<210> 366

<211> 631

<212> DNA

<213> Homo sapiens

<400> 366

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agctggccca gatgtggaag gtggtgaatc tccaacaga tctgtttaat agtgtgatga 180
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cttcagaatg actgaaaccc atataccacc caaaatcaat tttcttgtac aactgggtaca 600
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```

<210> 367

<211> 1143

<212> DNA

<213> Homo sapiens

<400> 367

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gttgtgaagc cattaatata aatctttggt aatgaccac atctctatat gtatgtgttc 300
ccacttgtgg gagcaggcac taatgaaatc ctgtgcctgg aatggagata ttaggttacc 360

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tgaggcttag tgtcctgtgg tctgcatgta agatagatga catcctagaa caaagaagct 420
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agtgtctctgt gtactaaaca aaataaagcc cctctttgca tttaaaacca aagtcaaac 720
aaaactcttg taatgcaatt aattaaacttt atgtcttccc atgactcaag ttttggttaa 780
tatgcccata aactttgatt ggcagtttct tcggttaatt attcctatag aatgtatttt 840
aagaaatcta tacaaattgg atatatgctt ggtaattctc cagtttctag gaggtacct 900
tttctaccgt ttcaagtgat gaagtgaata taatttacat tcgatagtgt tactgataac 960
aaacctactt aagagatatg ttgcttttta ctttaaggat agtgttgata gataaattag 1020
aatgtataga taggtttgtg aaagtctaaa taatggttgt atagatatgt atatatggtt 1080
cacatatctg gatctgtgta tttgattttg tacttttaaat gtgacaaata aaccttttgg 1140
gag 1143

```

<210> 368

<211> 748

<212> DNA

<213> Homo sapiens

<400> 368

```

agttgtggtt taaaccagga gtgcgcgcgc tccgttcacc gcgccctcag atgaatgcgg 60
ctgttaagac ctgcaataat ccagaatggc tactctgac tatgttgata aggaaaatgg 120
agaaccagga acccgtgtgg ttgctaagga tgggctgaag ctggggctctg gaccttcaat 180
caaagcctta gatgggagat ctcaagtttc aacaccacgt tttggcaaaa cgttcgatgc 240
cccaccagcc ttacctaaag ctactagaaa ggctttggga actgtcaaca gagctacaga 300
aaagtctgtt aagaccaagg gacccctcaa caaaaacagc caagcttttc tgccaaaaag 360
atgactgaaa agactgttaa agcaaaaagc tctgttcctg cctcagatga tgcctatcca 420
gaaatagaaa aatctttccc ttcactcctc agactttgag agttttgacc tgcctgaaga 480
gcaccagatt gcgcacctcc ccttgagtgg agtgcctctc atgaccttg acgaggagag 540
agagcttgaa aagctgttta agctgggcc ccttcacct gtgaagatgc cctctacacc 600
atgggaatcc aatctgttgc agtctccttc aagcattctg tagaccctgg atgttgaatt 660
gccacctgtt tgctgtgaca tagatattta aatttcttag tgcttcagag tttgtgtgta 720
tttgtattaa taaagcattc ttttaacag 748

```

<210> 369

<211> 550

<212> DNA

<213> Homo sapiens

<400> 369

```

tgagaagac ctagaattta aagaacaaaa ggaacgtgaa gatgagtctt cctctatgtt 60
tgacgaatat tttcaagaat gccaggatga atgaagagtt tactaaaagt aacctcttaa 120
agagcttggt gccaaaccag cagaacattc ttctcttcaa aggatgcaat agtagaaagc 180
tacttatttt aatgaaaaaa agtaaaactt cgttctttat cagcctcatg cctgaatcaa 240
atttttaatt attctgaaac tgctgctgtt taaagtggaa tcttttagta ttataacagc 300
atcacttttag attttgtaag tcaaaattga aatgaatgca catagattta tatataaatt 360
agcacctgag ctaagggtta ggctgggtcta aacttatttt cactttttgt attatttttg 420
agatgcagga attactgtta caaaatatgt atgtccgaag ggaaaaagct gcaaggatat 480
atataagacc accgcctatc tgtatcttcc caatttccta tattgaaaat gtatattatt 540
tatataaactt 550

```

<210> 370

<211> 651

<212> DNA

<213> Homo sapiens

<400> 370

```

aaatatacag tcttccact tcaactaacca aattcctact ttccagtgtt acttcccaat 60
ttatgcagga aacctcctgc aaagctgaaa ctgattagaa aattctttat attttaaaat 120
agctctttct catttttaga gaagtcaaat agccaaccat caaaattaag aataaattga 180
attgtcacag tccattacag ttattgttgc tagatccacc tcatttgcag atgtccaaac 240
ttaaattcat ctgttcttaa aatgctactt aaaactttgg ttgttttctt gtaatatata 300

```

```

agaaaaagtt aatttatcaa ttgattgaat acagttttta ctaattagtt tatcaaacca 360
aatactgtga acgtaccagg tgtttacaga tttaaatgca tgttaccata gaaactatta 420
aagtaactag aactgtcaaa taacaaaacg gctcatgttt ttaaaatata tgtaactcat 480
tttaaaatat attaaattgt attccaaacc tgttctctctg tttctgtggc acctaggttt 540
aaaatatgta ttaatgtgta aatcacaaagt aaaatgaatt ctaatgtaca agtttgtttt 600
aaaaagtgtg tgcaagctt ttatttacac aataaaatgt tattaagat g 651

```

<210> 371

<211> 635

<212> DNA

<213> Homo sapiens

<400> 371

```

ggttatttta aatataaata gctaattgggg gtggtaggcc tataaaatta aatgccttgt 60
ataaaatcca aaatgaatgc aaaattgttt tcacttgtat tgactttatg ttgtatgatt 120
ccaatctctg ttctgtttgg cacttgtatt taattcttca cttttgtaag acatttgtat 180
attgtggatg tgttcattca agctatttaa tatcttgac tgtaataca cagtacttta 240
ttgtacagac tgttttactg ttttaattgt agttctgtgt actttttttg gatggggctg 300
gcatgttttc tttgtttcct ggcaatacga cgtgggaatt tcaatgcgtt ttgtttaga 360
tgctaacgtg tcagaatccc ttacattcaa cttttctaaa aaaagcattt ccagtcctgt 420
agtgtgtgct acagtaacca aattgttgaa aatggtttca agttattcaa atttgtacag 480
gactgtaaag atatgttgac agcaaaatgt tgaaaaaaa agcctataga ataaaagcca 540
aaaagtatat attaggatct gcaacaatg aaaaattatg taatatattg tacaatgta 600
agcaaaagcc ctgaaataaa atgccatagt ttgtg 635

```

<210> 372

<211> 1192

<212> DNA

<213> Homo sapiens

<400> 372

```

cagtgtctga gtaaacatac gtgtgcgtgt gtctttatag tagcgtgatt tgtttaagaa 60
agtaacagag cagggattag agtccaagta atttggctcc agcactcctg cactacttaa 120
tacatttgtg tgttgtgta gtaataaat actgtacaaa tggcaagata ggccagacgc 180
tggtgtttca ataaagcaaa ctcatcttaa ccattgaaagt gactcagctt gagatttaat 240
taatatgtt tctatgtgtg aggatctttc tttttatggc ctttggcagt aaaatgatct 300
aagcgttttt atagaatgta taaaatgtgg ctttttttgt gtgttaaata ctttatgacc 360
ttgagtttac tgatcctgac gaagctcctc ttttctctt tttgcccact aaagatccat 420
tttatttatg cacacagtta aagccattgt agtgtagtgg aaacagcaca tattggattt 480
gtgtgttctt acattttaat tccagcatta tccattacta gctgtgtgac tggacaaatt 540
atacatctt agaacttccc ttttctaacc tgtaaaatga gggaaattaa atcttcttca 600
ttggatagtt gtaaggagta aatgggatga tatatttttt aaatgcctgc tgtactactt 660
actgtatggc agatattcaa aaaattgtga gtgctttact tcttaataaa tgaaacacgt 720
ccaaatttaa gtactttttt ttcccttata gttgctaaat tttgtagggt aactctgtgc 780
ttgccaaaca cttggtagcc agacctttag aatttgaacc agatactata gaggctcctaa 840
ataaaatatg cattagaaga gaaatgcata aattctttat ggtagtgtgt agactgtttt 900
gggtgtcttt gccaaagagt atttctctgc tgtatcggag gaggaacaat ggaaaggaaa 960
acttcagctt ctggtgtttc gggagtctta tcttgaagg ataaatgaat gaaaaaatga 1020
atcacatttt agttggacat gtaaaaagca agtagggaaa cttgggaaaa ttctcacaaa 1080
aggtagcttt ttttctaaaa aatttcttct tgatttttca gtaatgatgt agagagctgt 1140
agtttacaag ctgattttag aaccgtgtat taatgggaaa ggccaaagaa at 1192

```

<210> 373

<211> 1279

<212> DNA

<213> Homo sapiens

<400> 373

```

ttccaatagt ataaaaacat tgtagcgac tggacaatta cctcattcaa caatgtttca 60
aataatgtat tatattaaaa tgtagatgct gataagttct aagaaatatt tatacctttt 120
tatatggaag ataatttata tcatccatgt ttagtgcttt ttaaacatca actttacttt 180
ctaggtaatg tggctgtgca atattttttt aattttatct ttttactttt ctattacttt 240
ttcatatatt ttgtaccta agtatttcag tgaaacttta agcccatacc tgtgtctgat 300

```

```

gtttattatt ggctttccac aattcctaca tcagactaca ttatattaga gaccattatt 360
gctagaatag catgggattt aaaattttct aatactgggg gtattattta gttaattatg 420
gattttttctt ttacacatttt actgtgtttt taactgggaa ataagattat ggctgtctaca 480
atatattttt tgaaatccac ttctgttggt ctaaaataca actttatcat tgcaatccaa 540
ccaggtagtt catagaaaac tgtntttaat accagttttt ctataaagtc attactgttg 600
cttaaacata tttcatgcct attaaaaat attttctact ggtgatttca acattatttc 660
tcatactgac ttttattact ggaaatgttc ctgtacatgt tggcagcaga taaagatttt 720
tgaatgtttg aatgccctct gccttgattt ggttggaatt tttgctaaat tggtaatgtt 780
gcttgaactt tatgactaca ttttctttta acttttttca tggacttccc tatatgtaca 840
taataattaa atgttgaaat ttatgaaata cttttatgaa tttagataat ttttaaatat 900
tgttaaaatt tattgaacta aaaagtaatg tacataaaat aattcatgtt aaagatggaa 960
caaaaataatt aactttacat gtttggtgat acagatgcaa atgtttttga tatatggaga 1020
tggtgagtcct tttgacttta ccaaaggtgc tgaatagcat taaattcaca attttccttt 1080
tctgtttaac tagtgaaaat aaaaatgcac taaggttggg tccaagtctt gtttgcactc 1140
accaattgtg acagacagag gtttttgtaa gtattttatg tacaattgat gcatgtttat 1200
ttttagcggt gttattgcct ctggtgtaaa taaatgaaca aatggctatt tgggggaatc 1260
aaaaaaaaa aaaaaaac                                     1279

```

<210> 374

<211> 190

<212> DNA

<213> Homo sapiens

<400> 374

```

tacntttgca aatgtaatgg tggccgtggt gccatccgag aatttgcaga gcacatttgc 60
ctactaatgg aaaaggttaa taattcatgc caaaaataga aattagcgta atattgagaa 120
aaaaatgata cagccttctt cagccagttt gcttttattt ttgattaagt taattccatg 180
ttgtaatgtt                                     190

```

<210> 375

<211> 1377

<212> DNA

<213> Homo sapiens

<400> 375

```

tcatggccta cacaactagt ggaagtccat gtttagaaaa taaatggctt gtttaaggaa 60
aagtttttgt gtcctaaagct ccttaaagtc agagagattt ctacctggta cttaacatca 120
tatggaaatt gatgcttttag tgaggggtgt ggctatccta ttgtcaattt cctgcacatc 180
tttttcttct ttatttttgt atagagacaa ggtctcgtca tgttgcccag gctgggtctt 240
ttcctgggct caagcagtc tccgcctcgt gtctcccaaa gtgccgggat tacagggtgt 300
agccactgtg cccagcttat ccttttttca ttacacaaaa agactgaatt tggtttagtt 360
taagttggaa gataaagatg gtatgcacag gaggcccttg ggagccctca gataactttc 420
tcattcttcc aaaatcaggc tgggatgcat tctgtaaatt ttccctgcct aggatgtata 480
cctgaggaat aaggtaagga agatgtcagc aagtcagcct ctggtttacc tgctagctgg 540
catggatcct taaggaagca ggagggagtt ggggaagagag gaaggggtga agttgggtatc 600
ttttaaaagc agagtgtatt tacctcagat tttgaagaat actaaggaat ccagttgttg 660
gggtacatgc tattattaga aggatctaga taatttgtcc tctgagtcac acttgacatt 720
gtacctgtgg cacatcaatc cgcactgttt gatactctgg ctgaatctca gctttcacca 780
acattgtcaa aggacctttt ttagtgccca gccatgccta agagtgtgtc atctgaagag 840
ggaagcatct gcatactgct gtccctgattg ctcagtcttc actacctacc agaccggttg 900
gtaaggtaca aaagtacatg cttggaaaag cagtctgcac caccagtgat aagctgtgac 960
agagtggaac agcctcaatg aaatgaagga aggatgtcta cagtggcatt aaggatggtc 1020
tcttaatcct gtgttaacca ctgattaac tttacaatca actcaaaatc cttcaaaggc 1080
tttccacttt ctttagtggc attcagacct cctctagtgt gaccctacc tccaacttga 1140
acctctgtta ctcttccgta tgaacatttt cctctagccc tggactacta gtaccgaagt 1200
cactagtca ataggactca tttgaaatat gactagtctc aattgagatg taatgtaagt 1260
gtaaaataca cagcagattt ctaagacagc acacaaaatg taaaatatgt caaaaatatt 1320
tgatactgat tacatgttga aatatatgtt ttgggttaaa taaatgcat taaagtt 1377

```

<210> 376

<211> 489

<212> DNA

<213> Homo sapiens

<400> 376

```

gctcttgcca tggccctgca gcctggtaca ctgcaactga taccaaagag atcagcactg 60
gaaaagccca atggtgccaac cccggtcttt aatcccactg ttttccactg ccaacagggt 120
ctgactaacc tgcagctccc acagccggca tttatccctg cagggccaat actgtgcatg 180
gcacccgctt caaatattgt gcccatgatg caccgtgcta cacctaccac tgtgtctgca 240
gcaacaacac ctgccaccag cgttccgttc gctgcaccaa ctacaggcaa tcagctgaaa 300
ttctgaacag cagagttatg gagtatcaga atctttccat ggaaacctcc atatggcctt 360
tctatatata ttctcgtatg tcttattcta ccaacacaac aataagcgtg ttgcagtcaa 420
tgtattaagc aaagcaaacc tgccagccag caaattcaaa taaaaaata aagcattaaa 480
aaaaaaaaag                                     489

```

<210> 377

<211> 372

<212> DNA

<213> Homo sapiens

<400> 377

```

cccgattgaa ttctagacct gcggcngctt ttttttcaca ttttaattga atatctacag 60
taggaagggt cttacaatca atgatgtgtc atggtgtaat ttttttttct ttctccctaa 120
tacataaaat aagtgggaagt tttacaatca ttggtgtctt aggatcagtg agatacagca 180
tgattttccc cgtgtctcag gcctgcttcc ctgagctctc caatggcagg aaccacgtgg 240
tggttctcct cagagctctg ggctcagcct ccagaactgg gactgagcta aagagtcact 300
aaatggtcac tgagatcagg agcagaattc cctgagagtt gcttatctct gggaacctga 360
cctgtccaaa tt                                     372

```

<210> 378

<211> 558

<212> DNA

<213> Homo sapiens

<400> 378

```

agaaagagca actttgtttt aactctgcta gatactggaa aacccatgga actaatgaag 60
agcctagggc tttttatttg ttttgagatt gtgccatttc actccagcct gggcaacaag 120
agagaaactt tgtctcacac acaaaaaaag tgtaaatcaa aacattaaaa attaatgagt 180
ttggaagtag attatcaaaa aggtcctgaa agggagggtc tttggctata atctttaacg 240
caactctaca ctccctgtat ggagacagat ttctttctag atggttacag tcacaaaagta 300
gggttttcag tagcatttag ggatgaatga atcttgcagc acctctccat gtatcttget 360
agccccctct aaacttcagg tcagtttagtg ctctctcaga aattgttccc cccacaccaa 420
gtttccacat ttacagttat actgatatcc acattgtact gttgtatgtg acacctagat 480
tataggaaat tttggctata gatcagaaat taactgctat gttttgcctt tacgctaaag 540
agattttgtt tgtttagt                                     558

```

<210> 379

<211> 993

<212> DNA

<213> Homo sapiens

<400> 379

```

atttatcaaa tcttatttct tcccactccc ccatttgtac agccacagca tgggaaacaa 60
atgggggagt gggaagaaat aagatttgat aaatagttca gggcaacatg atagaagggc 120
atgtacatca tgctaaaaaa aagtgattgc tttttgtggc aaggaagaac aataaaaatt 180
tagaaatatt tattaggtgt ctattctgtg ttaataatgt acaatacat tctggggata 240
atgagctgaa aaaggatatg ggcctcatgt gtatcacagt gcaacaagaa accaattcct 300
gagacagaaa caattggtaa aggagcacat ttgggtcatgc ctgtaatccc agccttgtcc 360
tcatcgtctt cttttccacc ctcttttctc ctccacgttt tcttccactg tcttctctac 420
cacactgtct tctccctgca ctttctcccc actgtcttct tccccacctt tctccccatc 480
ccactttcca aggtcttttc caccctctcc gtccccctct cccctctctc ccgcagtctt 540
ccggggcccca ctgtctttcg ccgcagccca aactgtttca gttctgaggt atcggcaggg 600
gcgggggagg cggcagccgt gatggccctg gcagcgactc tcctgggtct cctgttggct 660
gttggggcgg agctcagggg cccagctcat ggggctggct gggcgacag acacaccagg 720
cgcagggaca caggcgggag cagcgttgga gcgcttctag gtgaaaggca gttggagagc 780
gcgagaaggg ggtgggcaag aagaagatcg gggcgaagac ggtggggagt ggaagagggg 840

```



```

agaagaggggt gcggggagag aaaaacgcgg caggaagtcg ctgctgcgag aaggtgggga 900
ggggaagaag atggcggaga ataagaggct ggggaaaaaa gacgatggga gggggagaga 960
agaaagtggg aagaagaatt gaattctata cct                                     993

```

```

<210> 380
<211> 786
<212> DNA
<213> Homo sapiens

```

```

<400> 380
gggaagaaga aagttgagct ttttccctt gagaaacttc tgcatttagt ttctatcttt 60
ccaggcaaaa caaatgggta ttcttttcat acaaccattt tcaaataaac cttagaaaag 120
tcttaacatt taaggatatt tatgcacaga atacacttag attgatagga aagaactcgt 180
aatggagttt gagtaaagaa aatgactgat gtactaaacc cagtaaaaaa tgttgaaaat 240
gttaaagggtc agcatgttct aattgggaat ctatatatag cttagatttc ctattggctt 300
agagtatttg ctataacaaa tgaagtgcaa tgacaattat atattcctac tcggtcatac 360
tggactggct tcgttctctt aatatactca gtaatgactc aagcctctgg ctattaacat 420
accctagttg ccgtttttta attgccatga gccaaatact tottggtata caattgatcc 480
atattatttt atggctgcct tttcattttc atcttttctt gctgctaccc atctatgtat 540
gtagtcaattg gggggaaaat gtagccacat tttttatggg aagactttgt gttaaaagtg 600
aacatttttg aggtttttta ctggtgaaac tagcctggaa taatgccacc agagactgag 660
tggaaatcgc cccttttgaa ggtgccattc ttatgagcca aaagtttgtc atttaaaagt 720
tcattttgag ggaataacat gtaatatgat ttgaaataaa ggtatggtga agttgacacg 780
caaagt                                             786

```

```

<210> 381
<211> 329
<212> DNA
<213> Homo sapiens

```

```

<400> 381
ggcagcgcag ccctgactat actggtagaa tgctgggatg ggcacctgac accccctgag 60
gttgcatccc tggctgacag ggcatacacg gcaagagact ccaatatggt gagggcggca 120
gcagagctgg ccctgagctg cctgcctcac gcccatgcat tgaaccctaa tgagatccag 180
cgggccctgg tgcaagtcaa ggaacaggac aacctgatgt tggagaaggc cgcaattcta 240
acgttactgg ccgaaccgct tggaataagg cccgtgtgcg tttgtctata tgtgattttc 300
caccctattg ccgtcttttg gcaatgtga                                     329

```

```

<210> 382
<211> 364
<212> DNA
<213> Homo sapiens

```

```

<400> 382
gcttgtcaga gcagggattt gcatcacaga ctggccactg caaagacaga tgggaactca 60
cagggttttgt gtgtgtgttt gtggttctact gctgatggac gcatgnnaga agccacctga 120
gccttggccc agccttcatg tggagtgaaa acccagacct gtgtgagcag caggtagttg 180
aagcaagaga agcaaggcgg agccaccagg gctttgttag aggcctcttt ctccctggaa 240
accaattgaa caaccaggag ccagaggtct tgggtggccg atgtgggtct aatcctgggt 300
ccatggtctc ccaactgagt gaatgaaaaa aaaaaaaaaa aaaaaaattt actgtgtacc 360
cggc                                             364

```

```

<210> 383
<211> 590
<212> DNA
<213> Homo sapiens

```

```

<400> 383
tgtaaatgg agacagtaat agcacagatt aagttgctga gttatgaaga tctgattaga 60
ttatgcatgt gaaagcaata ggccgggcct cctctgcgta atcttatttc taattttaag 120
agccaggaac ccactttttt ggagcctgat gttctaatat tccttcctta cgaaagccag 180
gtcattgctt ttttcatctg cctgatgcac tgtaagagcc ttgtgtgttc tttcaaaagc 240
gatctctcat atttctcgtt tttgggtctt aggtgtcttt tcatttggca atcttcgtcc 300

```

```

tacagagggc tggaaaaact gcagaagacg gcatatccac caccgcgtgc tgggtcggcc 360
ctgcagctgt gtgcacccaa gaactgccaa agaagctggg tcttggcgcg gcggaacgga 420
ccaatcagaa aaagtttggc cctctgcagt ttccgtccgc tcactaggag gcgtgcggc 480
agcgacggcg gcgtcggcgg cggcggggcg tgtcgggggt tggggcggtt gggctggcag 540
ctgaggctcg tggccatgga gtgggggttct gagtgggggt ctgtgaggcg 590

```

<210> 384

<211> 581

<212> DNA

<213> Homo sapiens

<400> 384

```

gcattaaatt catttgtttt tatatcagat tcacactctt attttaactt tataatat 60
actgatattt agtaggtcta atgtcttttt ctctttttcc ttctctttaa atatttatct 120
cttcttgccct gtttaacatt tcaaatcaat tttagaacca atttttcaag ttccaaaaca 180
taagcaaaaca gaaggaaaaa cctcaacgaa accttctggg gtttggattg tgtattat 240
agggtaagga atatgtgctg ctttagcaaa tgaacttgaa aatcttttat agggccgggc 300
gcgggtgacac atgcctgtaa tcccagatac ttgggaggct gaggcaggag atcgcttgaa 360
ccgggaagca gaggttgcac tccagcccg ggcagagagc ggcggcggtg gggggtgggg 420
gggaagcaaa aaacaaatta gctgagtata gtggtgcacc tgtaatccta gctactcagg 480
aggctgaagc acagggattg cttgaacccg ggaggcagag ttgcagttag ccaagatcat 540
gccactgtac tctagcctgg gcaacagagc aagactgtct c 581

```

<210> 385

<211> 502

<212> DNA

<213> Homo sapiens

<400> 385

```

ctagtatgaa tgaaaaaaaa aaaaaccacc aacatttcat aaacatgact ccctgcagcc 60
gatctggtcc cgacatgggg gtggatccca gaagcgggag acagccttcc acggaaactt 120
gcaaaactgc accaaaatct atcaattttg aaaatgctct tgaattcttg gcggaagaaa 180
gatgctgata aacacattaa gtggggaaat gctcccttga gaaaggctgg gttggctcta 240
tgaagacacc tttggagtga gctgtgcctg ggagaaacc cttctgtgctt ttcccttcat 300
tcaccggaga tgaggctgag tgttcaagta aacaggaagc ttacctgtgg tgggtcaaatt 360
acaaacactc aacatggcac ccatgaataa ttagaaaata caagcgccga agtgacgggg 420
gcgggagcta ggaggcgag gggaaacaga acaatcttgg aaaaatctcg gttgttgcaa 480
aaaaagaata aaatgtatgc gt 502

```

<210> 386

<211> 271

<212> DNA

<213> Homo sapiens

<400> 386

```

aatactagca ctgttgtata aaaccctgtt tggagtacgc ataactgaaa ccaaaactct 60
aacaaatttt gagagccttg taaattgaaa ctacgtgaga ttgatactta aatcccaaaa 120
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<210> 387

<211> 1054

<212> DNA

<213> Homo sapiens

<400> 387

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```

```

gcgcaagccc acctagaccg cagaggcgcc gtcattccaga gcgtccctgg cttctgggcc 420
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gattgtntgg aatgaaaaat aaacattctc aagg 1054

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<210> 388

<211> 366

<212> DNA

<213> Homo sapiens

<400> 388

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gtgtggccga gagctatgac acggagagcg gcttcgagga tgcagagacc tgcgacgtag 180
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tcaccagcga ccacctcaag gggctgcatg tcatggtgcc agacattgtc cagatgcaca 300
tcgagacctt ggaggccgtg cagcgggaga gccggaggtg ccgcccatcc agaagcccaa 360
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<210> 389

<211> 690

<212> DNA

<213> Homo sapiens

<400> 389

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tccgaaaccc catgatgtct aagcttcgaa actaccggaa ggaccttgct aaactccatc 60
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gcatatatgc ttagagaat gagcatatga atcggctaca gtctcaaagg gcaatgcttc 180
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tanccaggct gtgggaggag ggaggaaaga tgaaaaacca cttaaatgtg aaggaacaac 660
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```

<210> 390

<211> 1844

<212> DNA

<213> Homo sapiens

<400> 390

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```

```

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<210> 391

<211> 1259

<212> DNA

<213> Homo sapiens

<400> 391

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```

<210> 392

<211> 587

<212> DNA

<213> Homo sapiens

<400> 392

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caggatcgtc tcaagccaga catgtgaacc actcagccac tgaggctctc ggagaactca 120
gggaaagagc ccctgggcaa ggcacaaacg ggtttcagct gctacgccac gcagtgaac 180
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tgccattctg gtgagaaaaa cgttgacatt tgcctctgat cctggaatag gtgttgcta 420
tcaaatatag atgaagaagg aaaagagaaa ccagagatgg gtggccgaac tgggatctaa 480

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aatataagct cccggaaggc agggatgttg aagtatccca agggcttaaa ggaatgtgtg 540
gcttattgta ggtgttcaat aaatatttgt tgaatgaatt tagcacc 587

<210> 393

<211> 1935

<212> DNA

<213> Homo sapiens

<400> 393

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ctgttctggc tgaaggctta gcaaagatgt tggcagagga agcagagact gggctgggtc 1860
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<210> 394

<211> 357

<212> DNA

<213> Homo sapiens

<400> 394

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tggtgcctgc acctgcactc tagtgacctt ggggtgccgc agacccttct cttctacaaa 120
gacccagca ggagtgggag ggtctgcaat ggcctcgccc tgcctgcct tggccagaag 180
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acaggcagct gttgagctcg ggggtgtctc cccaaggcat gtggctcagc agcaagaaag 300
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<210> 395

<211> 1201

<212> DNA

<213> Homo sapiens

<400> 395

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<210> 396

<211> 1432

<212> DNA

<213> Homo sapiens

<400> 396

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<210> 397

<211> 439

<212> DNA

<213> Homo sapiens

<400> 397

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gcttcagtgt gaaaggccac gtgaagatgc tgcggctgga tattatcaac tcaactggta 180
caacagttat catgctcatc gtatctgtgt tggcactgat accagaaacc acaacattga 240
cagttgggtg aggggtgttt gcacttgtga cagcagtatg ctgtcttgcc gacggggccc 300

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```

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tattttctgta ttcttcccc                                     439

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<210> 398
 <211> 657
 <212> DNA
 <213> Homo sapiens

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<400> 398
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<210> 399
 <211> 1845
 <212> DNA
 <213> Homo sapiens

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<400> 399
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<210> 400
 <211> 642
 <212> DNA

<213> Homo sapiens

<400> 400

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<210> 401

<211> 1361

<212> DNA

<213> Homo sapiens

<400> 401

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<210> 402

<211> 2547

<212> DNA

<213> Homo sapiens

<400> 402

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<210> 403

<211> 1010

<212> DNA

<213> Homo sapiens

<400> 403

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<210> 404

<211> 946

<212> DNA

<213> Homo sapiens

<400> 404

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<210> 405

<211> 3028

<212> DNA

<213> Homo sapiens

<400> 405

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<210> 406

<211> 329

<212> DNA

<213> Homo sapiens

<400> 406

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<211> 1622

<212> DNA

<213> Homo sapiens

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<210> 408

<211> 1202

<212> DNA

<213> Homo sapiens

<400> 408

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<210> 409

<211> 425

<212> DNA

<213> Homo sapiens

<400> 409

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<211> 907

<212> DNA

<213> Homo sapiens

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<211> 559
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<210> 412
 <211> 1555
 <212> DNA
 <213> Homo sapiens

<400> 412
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 <211> 634
 <212> DNA
 <213> Homo sapiens

<400> 413
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gcagttcaga ggttgcaata cttagtatag taaataaata aacggtcaac attgtgcaac 540
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<210> 414

<211> 688

<212> DNA

<213> Homo sapiens

<400> 414

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<210> 415

<211> 1156

<212> DNA

<213> Homo sapiens

<400> 415

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<210> 416

<211> 569

<212> DNA

<213> Homo sapiens

<400> 416

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<210> 417

<211> 1281

<212> DNA

<213> Homo sapiens

<400> 417

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<210> 418

<211> 580

<212> DNA

<213> Homo sapiens

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<210> 419

<211> 712

<212> DNA

<213> Homo sapiens

<400> 419

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<211> 608

<212> DNA

<213> Homo sapiens

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<211> 2843

<212> DNA

<213> Homo sapiens

<400> 421

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<210> 422

<211> 382

<212> DNA

<213> Homo sapiens

<400> 422

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<210> 423

<211> 2957

<212> DNA

<213> Homo sapiens

<400> 423

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<210> 424

<211> 1515

<212> DNA

<213> Homo sapiens

<400> 424

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gtgtcagttg ctttg
1515

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<210> 425

<211> 320

<212> DNA

<213> Homo sapiens

<400> 425

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ttatatcttg agttactaac taaccacgcg tgttggtcct atgtgctttt ctttcatttt 240
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<210> 426

<211> 2054

<212> DNA

<213> Homo sapiens

<400> 426

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<210> 427

<211> 571

<212> DNA

<213> Homo sapiens

<400> 427

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aatcactaaa agtactttgc catattggaa cctgaggcaa aaagaaaaat aagtaataat 480

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<210> 428

<211> 708

<212> DNA

<213> Homo sapiens

<400> 428

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<210> 429

<211> 625

<212> DNA

<213> Homo sapiens

<400> 429

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<210> 430

<211> 2979

<212> DNA

<213> Homo sapiens

<400> 430

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<210> 431

<211> 2299

<212> DNA

<213> Homo sapiens

<400> 431

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<210> 432

<211> 1257

<212> DNA

<213> Homo sapiens

<400> 432

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<210> 433

<211> 893

<212> DNA

<213> Homo sapiens

<400> 433

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<210> 434

<211> 807

<212> DNA

<213> Homo sapiens

<400> 434

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ggaagtaaac atttaanatt tataggactt cctctggcat gtaggtatga tattagaaga 780
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<210> 435

<211> 442

<212> DNA

<213> Homo sapiens

<400> 435

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<210> 436

<211> 870

<212> DNA

<213> Homo sapiens

<400> 436

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<210> 437

<211> 655

<212> DNA

<213> Homo sapiens

<400> 437

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<210> 438

<211> 814

<212> DNA

<213> Homo sapiens

<400> 438

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<210> 439

<211> 450

<212> DNA

<213> Homo sapiens

<400> 439

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caattatgtt aataaataag acaatgctac 450
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<210> 440

<211> 567

<212> DNA

<213> Homo sapiens

<400> 440

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<210> 441

<211> 956

<212> DNA

<213> Homo sapiens

<400> 441

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<210> 442

<211> 1804

<212> DNA

<213> Homo sapiens

<400> 442

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<210> 443

<211> 642

<212> DNA

<213> Homo sapiens

<400> 443

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<210> 444

<211> 2592

<212> DNA

<213> Homo sapiens

<400> 444

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<210> 445

<211> 2092

<212> DNA

<213> Homo sapiens

<400> 445

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<210> 446

<211> 1266

<212> DNA

<213> Homo sapiens

<400> 446

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atgggagaaa cagaaacatg ggagaaagag gtaagggaga cctaggggaa gaaagacaaa 180
ggaaaagagt ttaaagtttg gaggttaactt tgccagaggt cacattctgc tagtcataag 240
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gacttaacct ttcagaacct cagttatctc ctctgtaaaa cagataaggg cacctctctc 480
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<210> 447
<211> 1446
<212> DNA
<213> Homo sapiens

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<400> 447
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1446

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<210> 448
<211> 697
<212> DNA
<213> Homo sapiens

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<400> 448
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cctgttggtc ctggcctggc cggggaagg ggcagcgga ccggactgac ctgcagtac 180
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gctgcgtcgt ttcgatatca caccctctgt ttgcccctt acttctgct tcgagaatgt 420
ataacgtgga aatccacggg accaaatttc tgcagaggcc ttgccggtg gttccataac 480

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tgtagagtct aattgctatc cattacagaa attaatcgtt cagttgaaag aagtactgat 540
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gttagtgctt atttttgcat gttgatgttg actagctaata aaactgtaaa tgtaaaccat 660
gcgaataaaa tggttttcta tttctcattt ccgtgtg 697

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<210> 449

<211> 1354

<212> DNA

<213> Homo sapiens

<400> 449

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tccaaataaa gcaaaatcat gctttcacct gcct 1354

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<210> 450

<211> 1044

<212> DNA

<213> Homo sapiens

<400> 450

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aaaggtaaat ggaacaagaa atttgtcagc taccatatca aaacatctag caggccaggt 120
gtgggtggct gtgcctgtaa acctagcact ttgggaagcc aaggtagggag gactgcttga 180
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<210> 451

<211> 1133

<212> DNA

<213> Homo sapiens

<400> 451

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<210> 452

<211> 1393

<212> DNA

<213> Homo sapiens

<400> 452

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<210> 453

<211> 925

<212> DNA

<213> Homo sapiens

<400> 453

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atggctgggtc ttcatagtag tcagctcttg actttgcttc tgtttttttt ttttctctcc 180

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<210> 454

<211> 553

<212> DNA

<213> Homo sapiens

<400> 454

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<210> 455

<211> 1233

<212> DNA

<213> Homo sapiens

<400> 455

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<210> 456

<211> 1393

<212> DNA

<213> Homo sapiens

<400> 456

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<210> 457

<211> 471

<212> DNA

<213> Homo sapiens

<400> 457

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```

<210> 458

<211> 1429

<212> DNA

<213> Homo sapiens

<400> 458

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```

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<210> 459

<211> 1743

<212> DNA

<213> Homo sapiens

<400> 459

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<210> 460

<211> 2135

<212> DNA

<213> Homo sapiens

<400> 460

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aggagagaaa ggagatcatg tatgcaaaaa gtagaacatt tctcccttc ctattttgtc 180
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<210> 461

<211> 1226

<212> DNA

<213> Homo sapiens

<400> 461

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<210> 462

<211> 970

<212> DNA

<213> Homo sapiens

<400> 462

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```

ggccgcgagt tgcaggcatt gaggtagcag ttgggcccgg agtacggcaa gaatttggcc 240
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<210> 463

<211> 563

<212> DNA

<213> Homo sapiens

<400> 463

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<210> 464

<211> 1138

<212> DNA

<213> Homo sapiens

<400> 464

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<210> 465

<211> 775

<212> DNA

<213> Homo sapiens

<400> 465

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<212> DNA

<213> Homo sapiens

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<211> 1422

<212> DNA

<213> Homo sapiens

<400> 467

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<210> 468

<211> 1727

<212> DNA

<213> Homo sapiens

<400> 468

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<211> 1088

<212> DNA

<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

<400> 475
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tatgtgtgtg acttacattt ttgttctggg taagcataga gagaaaactc ttaactttgt 240
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tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtctcatat atatagtcta taatagctaa 540
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gcagggtcagt tgtaataaat ctaggatgtg atgatgacta tgtaatttga ttttctgaaa 1020
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 accaggg 1087

<210> 476

<211> 504

<212> DNA

<213> Homo sapiens

<400> 476

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 agaatttaaat attgatacaa tttcacctct aaaatggatt tgaagaaatg caactttata 180
 tcaaaaaatg tcatctgatt tcctttgttt cttttttaa ttatgtaatc agatgatttt 240
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 taaaatacca aactgtaact gactacagtg ggatcgtttt ctgttaggat gttaatatta 420
 tacaatgaaa tctataaagt gttgtcaatt tgattattga cacatataac atgtttacaa 480
 ataaactgtg gtattgatca agtt 504

<210> 477

<211> 404

<212> DNA

<213> Homo sapiens

<400> 477

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 taagtattaa cagaagagaa aaatgaaacc gtggggagat taaataacag gaagtttaca 180
 ccacagcaag ggtgctcacc catcccaatt tggggggaca cacaagtgaac tattgggtga 240
 aatagaccog atcatgcaaa tcatcgtatg atcacttggt atcctttggc agttctgaca 300
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<210> 478

<211> 2525

<212> DNA

<213> Homo sapiens

<400> 478

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 atattaattt ccaatcattt acatgttgct ttttaaagt tcttaggtc actttgggtg 180
 atgtggtctc cttctttctc catgttcccc taaagcttc acactgttga attatgtgcc 240
 tgtggcgacc atcctccagg aagggcacct tctgctgat gaggcaacca tgggttggtc 300
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tttcttctct tttctgcaga ccaggcaggc caccaaggtg ctgaacccca cgagggtgcc 1620
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ggtgg 2525

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<210> 479

<211> 544

<212> DNA

<213> Homo sapiens

<400> 479

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aactctgaac cgaatgtttt ggacttaact gttgcgtgca atatgaccgt cggcacactg 120
ctgttctctc agttccatgg acaggttctg ttttcaactt ttctgtatgca ctactgtatt 180
tcttttctaa ataaaattga tttgattgta tgcagtacta aggagactat cagaatttct 240
tgctattggt ttgcattttc ctagtataat tcatagcaag ttgacctcag agttcctgta 300
tcaggggagat tgtctgatcc tctaataaaa gacacattgc tgaccttggc cttgcccctt 360
gtacacaagt tcccagggtg agcagctttt ggatttaata tgaacatgta cagcgtgcat 420
agggactctt gccttaagga gtgtaaactt gatctgcatt tgctgatttg tttttaaaaa 480
aacaagaaat gcatgtttca aataaaattc tctattgtaa ataaaatttt ttctttggat 540
cttg 544

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<210> 480

<211> 543

<212> DNA

<213> Homo sapiens

<400> 480

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ctagaaccca ggagcgcaaa ccaccgttag ggctgaggg acgcagaggc ggggtgagta 120
gtgtttctca gattcgtggg aggcgcgagg cgccagcaga agcaattttc ctccctgag 180
caatgctagt tctcctcagg ccaggatct cactaacgt gtccttccac ctctcacag 240
gactccaagc tgctgtcccc tctctgccgc atctgaggct gggaaaactt cctaggagaa 300
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gcgcccaggc ccccgaaatg cctgccctcc ttctgacaaa aggagggggg aggatgtgaa 480
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tct 543

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<210> 481

<211> 482

<212> DNA

<213> Homo sapiens

<400> 481

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cgcgcgaggc cggaggcttg ggtgcgttca agattcaact tcaccggtaa cccaccgcca 60
tgcccgaaag aggcattgct gctggagggt taatggacgt taatctactgct ttacaagagg 120
ttctgaagac tgccctcatc cacgatggcc tagcactggg aattcgcgaa gctgccaaag 180

```

```

ccttagacaa ggcgcaagcc catctttgtg tgcttgcac caactgtgat gagcctatgt 240
atgtcaagtt ggtggaggcc ctttgtgctg aacaccaaatt caacctaat aagggttgatg 300
acaacaagaa actaggagaa tgggtaggcc tttgtaaaat tgacagagag gggaaacccc 360
gtaaagtggg tgggtgcagt tgtgtagtag ttaaggacta tggcaaggag tctcaggcca 420
aggatgtcat tgaagagtat ttcaaatgca agaaatgaag aaataaatct ttggctctcc 480
nn 482

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<210> 482

<211> 852

<212> DNA

<213> Homo sapiens

<400> 482

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gattaattgc tttatagtac aggtaaactt tgagaataag actatgtttc aaaaacagta 60
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tgcttatacc tgatgacttg gtttctaatt cattatgcga gtcagtgagc acctttaagg 180
gtttatgaca gtcatactaat tgtcttggtc agggccaaag gacttgggta tatgcttttc 240
ataccaaaat gacataattt cattgaggaa tctgcttatt aacccattcc cctaaaaatg 300
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acacctgtgt caagctgtac tctgtgtagt ataggtgacc ctcttctca aggaccggac 480
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ctccttgcct caacccaat tattcatttg acaaggaact gtctatcacc tactctgccc 600
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cacattgaat gtaccggatc attcattgaa tgatcactaa tggagagtta caaagcaatg 720
gggtctgaag gaaaggtaca gggttctatg agggaaatag ccaaggagcc tgatgcagac 780
tgggggctga gggacagctt cctgaggta atgtgacttg ggctgaacac ttaagaaagt 840
ggtgaaaact tt 852

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<210> 483

<211> 955

<212> DNA

<213> Homo sapiens

<400> 483

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gaatagtctg atgatctgac ttggttcctg tacgggtccag tttgtacata aacatttttg 60
tccatagggg cagtgcgtgt tactgatgca ggttgagagc tacaatggca ctatccaaaa 120
acaaaacgaa aaacctaca tggagcttgt tcctctgctg cattatgcag agatgggtct 180
caccccgctt tttcatgtga gaataagcac cttattcatt atagaaacat tgtgggtgtt 240
tcctgttact cattgctgaa tgcagtcctt cagtttattt tgaattatgt ttgagtacat 300
atgattacaa acaatataca tgtcctcctc aaacaaaagt tctctacaca tttcttagaa 360
atattaacag tatgcaagca acttgcatac tgtctgggta gttttgtatt tattgagaat 420
atatattaaa atatccatt ccaatcatgg atccgataaa ctttataatt aagctatttg 480
tccaacattg tgagtcaata ttactgtgag cttacaactt caggcctttt tttcctcata 540
aatttttagt ttcatgttta tttgattaca acttttatga tgatagtagt ttttcatatg 600
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cgggtggctc cctgtaatc ccagcatttt gggaggccaa tgcgggcaga tcacttgagg 780
ccaggaattg gagaccagcc tggacaacat agcaacacc tgtctctact aaaaatacaa 840
aaattggcct ggtgtggtgg tgcacatctg taatccagc tacttgggag tggaggttgc 900
agtgcgcaa gcacgccact gcactccagc ctgggcaaca gactgagact ctctc 955

```

<210> 484

<211> 488

<212> DNA

<213> Homo sapiens

<400> 484

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aacaatgac aaagtgtgaa tggaaaagcc tgctgttgtt ccacatctcg ttgctgttta 180
cattcctttg tggagcctac atcttcctaa gcttttttagc aggtatatgt tgaacacttc 240
tgtttcatgg ttgagacaga atcagaggcc atggatactg acaactgatt tgtctgtttt 300

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```

ttttctctgt ctttttccat gactcttata tactgcctca tcttgattta taagcaaaac 360
ctggaaaacc tacaaaaataa gtgttggtgt ttatctagaa aaatatggaa aatattgctg 420
ttatttttgg tgaagaaaat caattttgta tagtttattt caatctaaat aaaatgtgaa 480
ttttgttt                                     488

```

<210> 485

<211> 801

<212> DNA

<213> Homo sapiens

<400> 485

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gagcccccg agctgctacc gtggcgccgg cgctgtgagg agcagccagg gggaggcagc 60
tgcggctcgc cgggtgagtat ccgggaagcg ccaccatggg gctccgtaag aagagcacca 120
agaaccccc cggtctcagc caggaattca tcctgcagaa tcatgcggac atcgtctcct 180
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acatatccca gttggcttac tggtttcctg cttttcctga actctacttc cagaaaacca 660
aaaaacaaga catccctcgt caacttgtct acattgggtc tcacctcttc cacattactg 720
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ttgaattact ttcccacatg t                                     801

```

<210> 486

<211> 668

<212> DNA

<213> Homo sapiens

<400> 486

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cttgaacctc agcggcgagg gttgcagtga gtcgagatcg cgccagtga ctcagcctg 180
ggcaagaaga gcgaaactgg gtctcaagtt aaaaaaagaa agcaaggaaa gagtaattta 240
caacgaagga aaaaaaccca cagcacaccc ttgcgggctg tcagcgctct cctgatgtca 300
cagtggctgc gtgtccttgg ggtgggtgag gtgtggggag ccagcccct ggccctgcct 360
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ttaccaattt tgggaataaa aggtgttttg gttatttaat ataataagag ctgttaaact 600
tctgtttaaa tttccagttc aacttgtaaa tgtttttatt gtgcataaat acatactaat 660
gttgatct                                     668

```

<210> 487

<211> 852

<212> DNA

<213> Homo sapiens

<400> 487

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aatcatatga atcattagtg gttaatgttt gaaaaagctc ttgcaatcaa atctgtgatg 60
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tagtcggtag ggggcagctc tgctttatct atcctccatc tcaaaatgaa cttggaatta 180
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ttttgtctcc tgggtgattg gccaaagtct gggagtaagg agaggattag gtacttagga 660
gcaaagaaag aagtagcttg ggaacttttg agatgatccc taacatactg tactacttgc 720

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ttttacaatg tgttagcaga aaccagtggg ttataatgta gaatgatgtg ctttctgccc 780
 aagtggtaat tcatcttggg ttgctatggt aaaactgtaa atacaacaga acattaataa 840
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<210> 488
 <211> 367
 <212> DNA
 <213> Homo sapiens

<400> 488
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 tgaccgggac tccgtatctc tgaccacgat ggcgcttacc ttccagactt cattaaactt 360
 atgaccg 367

<210> 489
 <211> 1436
 <212> DNA
 <213> Homo sapiens

<400> 489
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 ctgtgactat caggtcctcg cgtgcccgcg gcatccaggc gttcagaaac tcgttttcat 180
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 ctaatgagaa agtgggctgg cttgttgagt ggcaagacta taagcctgtg gaatacactg 360
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 cgggtaggcc acttggccta tttactttca aaacaatttg catttagagt gtttcgcatc 1260
 agaataacat gagtaagatg aactggaaca caaaattttc agctcttttg tcaaaaggaa 1320
 tataagtaat catattttgt atgtattcga ttaagcatg gcttaaatta aatttaaaaca 1380
 actaatgtct tttgaagaat cataatcaga ataaagataa attcttgatc agctat 1436

<210> 490
 <211> 1460
 <212> DNA
 <213> Homo sapiens

<400> 490
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 tgaccactat ggtatatggt gggcaatgcc ctgccagtcc caacggtaga gaaaaatagg 120
 ccgtccccc caactctaca attaacatca gaggaattt ttacaagtt catcttacta 180
 tcaacttttta aaaagagaaa catctgtttg aaaatattct ctgtgatgat ttcttaatt 240
 cactttgaaa tcagtttctt actatgaagt cattaatgta agaacttggc caacaaagct 300
 tttcttctca taggctggct ctactagggg aactagtgtt tggtaaaact ctgggactac 360
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<210> 491

<211> 2614

<212> DNA

<213> Homo sapiens

<400> 491

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<210> 492

<211> 587

<212> DNA

<213> Homo sapiens

<400> 492

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<210> 493

<211> 772

<212> DNA

<213> Homo sapiens

<400> 493

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<210> 494

<211> 705

<212> DNA

<213> Homo sapiens

<400> 494

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<210> 495

<211> 426

<212> DNA

<213> Homo sapiens

<400> 495

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tctacatctt tttgtgtttt tggtaaaagc atgttcctta ggaggtaagc cattagtcac 420
ctttttt 426
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<210> 496

<211> 957

<212> DNA

<213> Homo sapiens

<400> 496

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<210> 497

<211> 1342

<212> DNA

<213> Homo sapiens

<400> 497

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<210> 498

<211> 1556

<212> DNA

<213> Homo sapiens

<400> 498

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<210> 499

<211> 772

<212> DNA

<213> Homo sapiens

<400> 499

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<210> 500

<211> 650

<212> DNA

<213> Homo sapiens

<400> 500

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<210> 501

<211> 6274

<212> DNA

<213> Homo sapiens

<400> 501

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<210> 502
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 <212> DNA

<213> Homo sapiens

<400> 502

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<211> 435

<212> DNA

<213> Homo sapiens

<400> 503

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accaattatc catct 435

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<210> 504

<211> 937

<212> DNA

<213> Homo sapiens

<400> 504

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<211> 476

<212> DNA

<213> Homo sapiens

<400> 505

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<210> 506

<211> 1073

<212> DNA

<213> Homo sapiens

<400> 506

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<211> 857

<212> DNA

<213> Homo sapiens

<400> 507

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<211> 569

<212> DNA

<213> Homo sapiens

<400> 508

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<210> 509

<211> 586

<212> DNA

<213> Homo sapiens

<400> 509

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<210> 510

<211> 2399

<212> DNA

<213> Homo sapiens

<400> 510

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<210> 511

<211> 1061

<212> DNA

<213> Homo sapiens

<400> 511

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<210> 512

<211> 836

<212> DNA

<213> Homo sapiens

<400> 512

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<210> 513

<211> 1087

<212> DNA

<213> Homo sapiens

<400> 513

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<210> 514

<211> 1116

<212> DNA

<213> Homo sapiens

<400> 514

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<210> 515

<211> 2082

<212> DNA

<213> Homo sapiens

<400> 515

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<210> 516

<211> 578

<212> DNA

<213> Homo sapiens

<400> 516

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<210> 517

<211> 486

<212> DNA

<213> Homo sapiens

<400> 517

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<210> 518

<211> 1433

<212> DNA

<213> Homo sapiens

<400> 518

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<210> 519

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<212> DNA

<213> Homo sapiens

<400> 519

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<210> 522
<211> 2269
<212> DNA
<213> Homo sapiens

<400> 522
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<211> 903

<212> DNA

<213> Homo sapiens

<400> 523

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<211> 490

<212> DNA

<213> Homo sapiens

<400> 524

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<211> 1307

<212> DNA

<213> Homo sapiens

<400> 525

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<210> 526

<211> 2010

<212> DNA

<213> Homo sapiens

<400> 526

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<210> 527

<211> 651

<212> DNA

<213> Homo sapiens

<400> 527

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<210> 528

<211> 539

<212> DNA

<213> Homo sapiens

<400> 528

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<210> 529

<211> 661

<212> DNA

<213> Homo sapiens

<400> 529

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<210> 530

<211> 363

<212> DNA

<213> Homo sapiens

<400> 530

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<210> 531

<211> 673

<212> DNA

<213> Homo sapiens

<400> 531

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<211> 317

<212> DNA

<213> Homo sapiens

<400> 532

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<210> 533

<211> 1193

<212> DNA

<213> Homo sapiens

<400> 533

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<211> 2229

<212> DNA

<213> Homo sapiens

<400> 534

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<210> 535

<211> 573

<212> DNA

<213> Homo sapiens

<400> 535

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<210> 536

<211> 470

<212> DNA

<213> Homo sapiens

<400> 536

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<210> 537

<211> 316

<212> DNA

<213> Homo sapiens

<400> 537

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aatctttcat tttcctatgt atgctttttt ccttttttgc ccagtttctt tatcacttgc 240
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<210> 538

<211> 1850

<212> DNA

<213> Homo sapiens

<400> 538

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<210> 539

<211> 2083

<212> DNA

<213> Homo sapiens

<400> 539

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<210> 540

<211> 1319

<212> DNA

<213> Homo sapiens

<400> 540

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<210> 541

<211> 1715

<212> DNA

<213> Homo sapiens

<400> 541

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<210> 542

<211> 350

<212> DNA

<213> Homo sapiens

<400> 542

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<210> 543

<211> 676

<212> DNA

<213> Homo sapiens

<400> 543

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<210> 544

<211> 605

<212> DNA

<213> Homo sapiens

<400> 544

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<210> 545

<211> 477

<212> DNA

<213> Homo sapiens

<400> 545

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<210> 546

<211> 970
<212> DNA
<213> Homo sapiens

<400> 546
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<210> 547
<211> 1303
<212> DNA
<213> Homo sapiens

<400> 547
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<210> 548
<211> 444
<212> DNA
<213> Homo sapiens

<400> 548
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<211> 779

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